

residue purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *cis*- *N*1-[4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzyl]-1-benzenesulfonamide acetate (0.042 g, 0.000048 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 8.18 (t, 1H), 7.79 (d, 2H), 7.63 (m, 3H), 7.58 (t, 2H), 7.26 (d, 2H), 7.09 (d, 2H), 7.01 (d, 2H), 4.78 (m, 1H), 4.01 (d, 2H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*_t 14.31 min.

MS: *MH*⁺ 653.

Example 258 *Cis*-*N*-[4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzyl]-*N'*-benzylurea acetate

Cis-3-{4-[4-(aminomethyl) phenoxy]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.051 g, 0.0001 mol) was dissolved in anhydrous pyridine (1mL), benzyl isocyanate (0.013 g, 0.0001 mol) was added and the resulting solution was stirred at ambient temperature for twenty hours. The solvent was removed under reduced pressure and the resulting residue purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *cis*- *N*-[4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzyl]-*N'*-benzylurea acetate (0.019 g, 0.000027 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.63 (d, 2H), 7.27 (m, 7H), 7.13 (d, 2H), 7.09 (d, 2H), 6.46 (m, 2H), 4.78 (m, 1H), 4.24 (d, 4H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*_t 13.49 min.

MS: *MH*⁺ 646.

The protocols to prepare *cis*-3-{4-[3-(aminomethyl) phenoxy]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and its derivatives

are identical to the ones for *cis*-3-{4-[4-(aminomethyl)phenoxy]phenyl}-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and its derivatives.

5 Example 259 *Cis*-*N*1-[3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzyl]benzamide diacetate

a) *cis*-3-{4-[3-(aminomethyl)phenoxy]phenyl}-1-[4-(4-

methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.63 (d, 2H), 7.38 (m, 1H), 7.15 (m,
10 4H), 6.96 (d, 1H), 4.78 (m, 1H), 3.73 (s, 2H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 9.32 min.

b) *Cis*-*N*1-[3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-
15 *d*]pyrimidin-3-yl}phenoxy)benzyl]benzamide diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 9.07 (t, 1H), 8.23 (s, 1H), 7.86 (d, 2H), 7.63 (d, 2H), 7.48 (m, 4H), 7.10 (m, 5H), 4.78 (m, 1H), 4.49 (d, 2H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 6H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.58 min.

MS: MH⁺ 617.

Example 260 *Cis*-*N*1-[3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzyl]-1-benzenesulfonamide acetate

25 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (m, 2H), 7.78 (d, 2H), 7.62 (m, 5H), 7.31 (m, 1H), 7.04 (m, 5H), 4.78 (m, 1H), 4.03 (d, 2H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.36 min.

30 MS: MH⁺ 653.

Example 261 *Cis-N*-[3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzyl]-*N'*-benzylurea acetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.63 (d, 2H), 7.35 (t, 1H), 7.27-7.04 (m, 10H), 6.46 (m, 2H), 4.78 (m, 1H), 4.25 (d, 2H), 4.22 (d, 2H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*_t 13.44 min.

MS: MH⁺ 646.

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Example 262 and Example 263

Cis-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-phenyl-1,3-oxazolan-2-one acetate

15

Trans-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-phenyl-1,3-oxazolan-2-one

a) 2-(4-bromoanilino)-1-phenyl-1-ethanone

To a solution containing 4-bromoaniline (7.42 g, 0.0431 mol) and 2-bromoacetophenone (8.58 g, 0.0431 mol) in *N,N*-dimethylformamide (200 mL) *N,N*-diisopropylethylamine was added dropwise and the reaction mixture was stirred at ambient temperature for five hours. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (150 mL) and water (100 mL). The organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The residue was suspended in diethyl ether and the precipitate was collected by filtration and dried to yield 2-(4-bromoanilino)-1-phenyl-1-ethanone (10.03 g, 0.0346 mol) as an off-white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.06 (d, 2H), 7.69 (t, 1H), 7.58 (m, 2H), 7.20 (d, 2H), 6.66 (d, 2H), 6.11 (t, 1H), 4.68 (d, 2H).

TLC (ethyl acetate / heptane 1:2) *R*_f 0.39

30 b) 2-(4-bromoanilino)-1-phenyl-1-ethanol

A solution of 2-(4-bromoanilino)-1-phenyl-1-ethanone (3.50 g, 0.0121 mol) in anhydrous methanol (200 mL) was cooled to 0°C and sodium borohydride (2.28 g, 0.0603mol) was added at once. The mixture was allowed to warm up to ambient

temperature while stirring under an atmosphere of nitrogen for three hours. The reaction was quenched by dropwise addition of acetic acid, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (120 mL) and water (85 mL). The organic phase was dried with magnesium sulfate and concentrated under reduced pressure to yield 2-(4-bromoanilino)-1-phenyl-1-ethanol (3.49 g, 0.0117 mol) as a yellow oil.

^1H NMR (DMSO- d_6 , 400MHz) δ 7.39 (d, 2H), 7.33 (m, 2H), 7.24 (t, 1H), 7.17 (d, 2H), 5.81 (t, 1H), 5.47 (d, 1H), 4.71 (m, 1H), 3.18 (m, 1H), 3.07 (m, 1H).

TLC (ethyl acetate / heptane 1:2) R_f 0.22

10 c) 3-(4-bromophenyl)-5-phenyl-1,3-oxazolan-2-one

A solution containing 2-(4-bromoanilino)-1-phenyl-1-ethanol (0.74 g, 0.00253 mol), *N,N*-diisopropylethylamine (1.01 g, 0.00786 mol) and *N,N*-dimethylaminopyridine (0.092 g, 0.00076 mol) in anhydrous dichloromethane (32 mL) was cooled to 0°C and a solution of triphosgene (0.38 g, 0.00127 mol) in anhydrous dichloromethane (8 mL) was added dropwise. The reaction mixture was slowly warmed up to ambient temperature while stirring under an atmosphere of nitrogen for eighteen hours. The organic phase was washed with a saturated solution of sodium bicarbonate in water (40 mL), brine (30 mL) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield 3-(4-bromophenyl)-5-phenyl-1,3-oxazolan-2-one (0.62 g, 0.00192 mol) as a white solid.

^1H NMR (DMSO- d_6 , 400MHz) δ 7.58 (s, 4H), 7.47 (m, 5H), 5.77 (m, 1H), 4.46 (t, 1H), 4.01 (t, 1H).

25 TLC (ethyl acetate / heptane 1:2) R_f 0.28

d) 5-phenyl-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolan-2-one

A mixture of 3-(4-bromophenyl)-5-phenyl-1,3-oxazolan-2-one (0.6 g, 0.00189 mol), diboron pinacol ester (0.58 g, 0.00226 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.046 g, 0.00057 mol) and potassium acetate (0.56 g, 0.0057 mol) in *N,N*-dimethylformamide (20 mL) was heated at 80°C under an atmosphere of nitrogen for sixteen hours. The mixture was allowed to cool to

ambient temperature and the solvent removed under reduced pressure.

Dichloromethane (100 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil which was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase. The resulting fractions were concentrated, the residue was triturated in n-heptane and the precipitate collected by filtration to yield 5-phenyl-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolan-2-one (0.19 g, 0.00052 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 7.69 (d, 2H), 7.62 (d, 2H), 7.47 (m, 5H), 5.77 (m, 1H), 4.46 (t, 1H), 4.01 (t, 1H), 1.27(s, 12H).

TLC (ethyl acetate / heptane 1:2) R_f 0.19

e) *Cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-phenyl-1,3-oxazolan-2-one acetate

A mixture of 5-phenyl-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolan-2-one (0.085 g, 0.000233 mol), *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.086 g, 0.000194 mol), tetrakis-(triphenylphosphine)palladium (0.013 g, 0.000012 mol) and sodium carbonate monohydrate (0.060 g, 0.000485 mol) was heated in a mixture of ethylene glycol dimethyl ether (5 mL) and water (3 mL) at 80° C for sixteen hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1 M ammonium acetate over 25 min, 21mL/min) to yield *cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-phenyl-1,3-oxazolan-2-one acetate (0.074g, 0.000121 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.79 (d, 2H), 7.68 (d, 2H), 7.47 (m, 5H), 5.82 (t, 1H), 4.78 (m, 1H), 4.57 (t, 1H), 4.09 (t, 1H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1 M

ammonium acetate over 20 min, 1mL/min) R_t 12.84 min.

MS: MH⁺ 553.

f) *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-

d]pyrimidin-3-yl}phenyl)-5-phenyl-1,3-oxazolan-2-one

The compound was prepared via synthetic route similar to the one for the preparation of *cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-phenyl-1,3-oxazolan-2-one acetate.

5 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.79 (d, 2H), 7.68 (d, 2H), 7.47 (m, 5H), 5.82 (t, 1H), 4.64 (m, 1H), 4.57 (t, 1H), 4.09 (t, 1H), 3.1 (br, 9H), 2.17 (s, 3H), 2.05 (m, 6H), 1.49 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.72 min.

10 MS: MH⁺ 553.

Example 264 *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-benzyl-1,3-oxazolan-2-one diacetate

15 a) 1-(4-bromoanilino)-3-phenyl-2-propanol

A mixture of 4-bromoaniline (1.75 g, 0.0102 mol) and 2,3-epoxypropylbenzene (1.77 g, 0.0132 mol) in methanol (40 mL) was heated at reflux for 16 hours. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield 1-(4-bromoanilino)-3-phenyl-2-propanol (2.2 g, 0.00719 mol) as a colorless oil.

20 ¹H NMR (DMSO-*d*₆, 400MHz) δ 7.33 (m, 7H), 6.50 (d, 2H), 5.76 (t, 1H), 4.83 (d, 1H), 3.82 (m, 1H), 2.98 (m, 1H), 2.90 (m, 1H), 2.78 (dd, 1H), 2.67 (dd, 1H).

TLC (ethyl acetate / heptane 1:3) R_f 0.29

25 b) 5-benzyl-3-(4-bromophenyl)-1,3-oxazolan-2-one

A solution containing 1-(4-bromoanilino)-3-phenyl-2-propanol (1.90 g, 0.00621 mol), *N,N*-diisopropylethylamine (2.48 g, 0.0193 mol) and *N,N*-dimethylaminopyridine (0.152 g, 0.00124 mol) in anhydrous dichloromethane (64 mL) was cooled to 0°C and the solution of triphosgene (0.92 g, 0.0031 mol) in anhydrous dichloromethane (16 mL) was added dropwise. The reaction mixture was slowly warmed up to ambient temperature while stirring under an atmosphere of nitrogen for 18 hours. The organic phase was washed with saturated solution of

sodium bicarbonate in water (70 mL), brine (60 mL) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield 5-benzyl-3-(4-bromophenyl)-1,3-oxazolan-2-one (1.25 g, 0.00377 mol) as a white solid.

^1H NMR (DMSO- d_6 , 400MHz) δ 7.54 (d, 2H), 7.47 (d, 2H), 7.27 (m, 5H), 4.95 (m, 1H), 4.12 (t, 1H), 3.78 (t, 1H), 3.07 (d, 2H).

TLC (ethyl acetate / heptane 1:3) R_f 0.37

c) 5-benzyl-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolan-2-one

A mixture of 5-benzyl-3-(4-bromophenyl)-1,3-oxazolan-2-one (1.25 g, 0.00377 mol), diboron pinacol ester (1.15 g, 0.00452 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.092 g, 0.000114 mol) and potassium acetate (1.12 g, 0.0113 mol) in *N,N*-dimethylformamide (30 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. Dichloromethane (100 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil which was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase. The resulting fractions were concentrated, the residue was triturated in n-heptane and the precipitate collected by filtration to yield 5-benzyl-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolan-2-one (1.03 g, 0.0027 mol) as a white solid.

^1H NMR (DMSO- d_6 , 400MHz) δ 7.65 (d, 2H), 7.54 (d, 2H), 7.27 (m, 5H), 4.95 (m, 1H), 4.12 (t, 1H), 3.78 (t, 1H), 3.07 (d, 2H), 1.28 (s, 12H).

TLC (ethyl acetate / heptane 1:3) R_f 0.25.

d) *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-benzyl-1,3-oxazolan-2-one diacetate

A mixture of 5-benzyl-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolan-2-one (0.110 g, 0.00029 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.080 g, 0.000181 mol),

- tetrakis-(triphenylphosphine)palladium (0.012 g, 0.000011 mol) and sodium carbonate monohydrate (0.056 g, 0.00045 mol) was heated in a mixture of ethylene glycol dimethyl ether (5 mL) and water (3 mL) at 80° C for sixteen hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-benzyl-1,3-oxazolan-2-one diacetate (0.049g, 0.000072 mol) as a white solid.
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.65 (m, 4H), 7.32 (m, 5H), 5.02 (m, 1H), 4.64 (m, 1H), 4.19 (t, 1H), 3.85 (t, 1H), 3.11 (d, 2H), 3.1 (br, 9H), 2.17 (s, 6H), 2.05 (m, 6H), 1.91 (s, 6H), 1.49 (m, 2H);
- RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1 M ammonium acetate over 20 min, 1mL/min) R_t 13.13 min.
- MS: MH⁺ 567.

Example 265 *Cis*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-2-methyl-2-phenylpropanamide diacetate

- A solution containing *cis*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.1 g, 0.000246 mol), α, α-dimethylphenylacetic acid (0.045 g, 0.000271 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.071 g, 0.000369 mol) and 1-hydroxy-7-azabenzotriazole (0.0037 g, 0.000271 mol) in anhydrous *N,N*-Dimethylformamide (5 mL) was stirred for 5 min., *N,N*-diisopropylethylamine (0.098 g, 0.00076 mol) was added dropwise and stirring under an atmosphere of nitrogen was continued for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *cis*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-2-methyl-2-phenylpropanamide diacetate (0.014 g, 0.000021 mol) as a white solid.
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.29 (s, 1H), 8.20 (s, 1H), 7.82 (d, 2H), 7.55 (d,

2H), 7.38 (m, 4H), 7.27 (m, 1H), 4.78 (m, 1H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 6H), 1.68 (m, 2H), 1.59 (s, 6H), 1.58 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.59 min.

5 MS: MH⁺ 553.

Example 266 and Example 267

Cis-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-4-oxo-2-phenylbutanoic acid acetate

10 *Cis*-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-4-oxo-3-phenylbutanoic acid acetate

a) 1-(4-bromophenyl)-3-phenyl-2,5-pyrrolidinedione

A solution of 4-bromoaniline (5.48 g, 0.0318 mol) and phenylsuccinic anhydride
15 (5.89 g, 0.0334 mol) in anhydrous benzene (80 mL) was heated at reflux for one and a half hours. The mixture was cooled to ambient temperature and concentrated under reduced pressure. To the residue, acetyl chloride (60 mL) was added and the solution was heated at reflux for one and a half hours. The reaction mixture was cooled to ambient temperature and the precipitate collected by filtration, washed with diethyl
20 ether and dried to yield 1-(4-bromophenyl)-3-phenyl-2,5-pyrrolidinedione (8.7 g, 0.0264 mol) as an off-white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 7.72 (d, 2H), 7.40 (m, 7H), 4.33 (dd, 1H), 3.33 (dd, 1H), 2.94 (dd, 1H);

TLC (ethyl acetate / heptane 1:4) R_f 0.34

25 b) 3-phenyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2,5-pyrrolidinedione

A mixture of 1-(4-bromophenyl)-3-phenyl-2,5-pyrrolidinedione (2.00 g, 0.00602 mol), diboron pinacol ester (1.85 g, 0.00727 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with
30 dichloromethane (1:1) (0.148 g, 0.000182 mol) and potassium acetate (1.784 g, 0.0182 mol) in *N,N*-dimethylformamide (40 mL) was heated at 80°C under an atmosphere of nitrogen for sixteen hours. The mixture was allowed to cool to

ambient temperature and the solvent removed under reduced pressure.

Dichloromethane (100 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil which was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:4) as mobile phase. The resulting fractions were concentrated, the residue was triturated in n-heptane and the precipitate collected by filtration to yield 3-phenyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2,5-pyrrolidinedione (0.78 g, 0.00207 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 7.79 (d, 2H), 7.40 (m, 7H), 4.33 (dd, 1H), 3.33 (dd, 1H), 2.97 (dd, 1H), 1.31 (s, 12H);

TLC (ethyl acetate / heptane 1:4) R_f 0.21

c) *Cis*-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-4-oxo-2-phenylbutanoic acid acetate and *cis*-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-4-oxo-3-phenylbutanoic acid acetate

A mixture of 3-phenyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2,5-pyrrolidinedione (0.35 g, 0.00093 mol), *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.34 g, 0.000773 mol), tetrakis-(triphenylphosphine)palladium (0.053 g, 0.000046 mol) and sodium carbonate monohydrate (0.24 g, 0.00193 mol) was heated in a mixture of ethylene glycol dimethyl ether (14 mL) and water (7 mL) at 80°C for sixteen hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *cis*-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-4-oxo-2-phenylbutanoic acid acetate (0.150g, 0.000233 mol) and *cis*-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-4-oxo-3-phenylbutanoic acid acetate (0.11 g, 0.000171 mol) both as white solids.

Cis-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-4-oxo-2-phenylbutanoic acid acetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.37 (s, 1H), 8.21 (s, 1H), 7.73 (d, 2H), 7.55 (d,

2H), 7.25 (m, 5H), 4.76 (m, 1H), 4.00 (m, 1H), 3.12 (dd, 1H), 2.71 (dd, 1H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.54 min.

5 MS: MH⁺ 583.

Cis-4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-
d]pyrimidin-3-yl}anilino)-4-oxo-3-phenylbutanoic acid acetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.46 (s, 1H), 8.21 (s, 1H), 7.78 (d, 2H), 7.54 (d, 2H), 7.41 (d, 5H), 7.31 (t, 2H), 7.24 (t, 1H), 4.76 (m, 1H), 4.16 (m, 1H), 3.08 (dd, 1H), 2.51 (dd, 1H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.11 min.

MS: MH⁺ 583.

15

Example 268 *Cis*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-
pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)(phenyl)methyl cyanide

a) 2-phenyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetonitrile A mixture of (4-bromophenyl)(phenyl)methyl cyanide (0.604 g, 0.00222 mol), diboron pinacol ester (0.677 g, 0.00266 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.054 g, 0.000067 mol) and potassium acetate (0.52 g, 0.00666 mol) in *N,N*-dimethylformamide (30 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. Dichloromethane (80 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil which was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:9) as mobile phase. The resulting fractions were concentrated, the residue was triturated in n-heptane and the precipitate collected by filtration to yield 2-phenyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetonitrile (0.110 g, 0.000345 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 7.67 (d, 2H), 7.40 (m, 7H), 5.87 (s, 1H), 1.31 (s,

12H);

TLC (ethyl acetate / heptane 1:9) R_f 0.18

b) *Cis*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)(phenyl)methyl cyanide

- 5 A mixture of 2-phenyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetonitrile (0.120 g, 0.000376 mol), *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.083 g, 0.000188 mol), tetrakis-(triphenylphosphine)palladium (0.013 g, 0.000011 mol) and sodium carbonate monohydrate (0.058 g, 0.00047 mol) was heated in a mixture of
10 ethylene glycol dimethyl ether (5 mL) and water (3 mL) at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *cis*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-
15 yl}phenyl)(phenyl)methyl cyanide (0.025g, 0.0000494 mol) as an off-white solid.

^1H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.70 (d, 2H), 7.58 (d, 2H), 7.47 (m, 4H), 7.38 (t, 1H), 5.93 (s, 1H), 4.76 (m, 1H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.68 (m, 2H), 1.58 (m, 2H);

- 20 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.95 min.
MS: MH^+ 507.

- Example 269 *Cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-
25 pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-1,3-benzoxazol-2-amine
 diacetate

a) *N*-(1,3-benzoxazol-2-yl)-*N*-(4-bromophenyl)amine

- 4-Bromoaniline (3.9 g, 0.0227 mol) was added to a solution of 2-chlorobenzoxazole (1.16 g, 0.00755 mol) in xylenes and the reaction mixture was
30 heated at 100°C for 2 hours. It was cooled to ambient temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL), the organic phase was dried with magnesium sulfate and

concentrated under reduced pressure. The residue was triturated in n-heptane and the precipitate collected by filtration and dried to yield *N*-(1,3-benzoxazol-2-yl)-*N*-(4-bromophenyl)amine (1.48 g, 0.00512 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.78 (s, 1H), 7.74 (d, 2H), 7.57 (d, 2H), 7.50 (m, 2H), 7.23 (t, 1H), 7.16(t, 1H).

TLC (ethyl acetate / heptane 1:3) R_f 0.34

b) *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-(1,3-benzoxazol-2-yl)-*N*-(4-bromophenyl)amine (0.800 g, 0.00277 mol), diboron pinacol ester (0.84 g, 0.00332 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.068 g, 0.000083 mol) and potassium acetate (0.81 g, 0.0083 mol) in *N,N*-dimethylformamide (20 mL) was heated at 80° C under an atmosphere of nitrogen for sixteen hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. Dichloromethane (100 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil which was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase. The resulting fractions were concentrated, the residue was triturated in n-heptane and the precipitate collected by filtration to yield *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.59 g, 0.00176 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.80 (s, 1H), 7.78 (d, 2H), 7.68 (d, 2H), 7.50 (d, 2H), 7.23 (t, 1H), 7.16 (t, 1H), 1.26 (s, 12H)

TLC (ethyl acetate / heptane 1:3) R_f 0.29

c) *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-1,3-benzoxazol-2-amine diacetate

A mixture of *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.073 g, 0.000217 mol), *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.080 g, 0.000181 mol), tetrakis-(triphenylphosphine)palladium (0.012 g, 0.000011 mol) and sodium carbonate monohydrate (0.056 g, 0.000453 mol) was heated in a mixture of ethylene

glycol dimethyl ether (5 mL) and water (3 mL) at 80° C for sixteen hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1 M

5 ammonium acetate over 25 min, 21mL/min) to yield *cis*-N2-(4-4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-1,3-benzoxazol-2-amine diacetate (0.082 g, 0.000128 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.95 (d, 2H), 7.66 (d, 2H), 7.51 (m, 2H), 7.25 (t, 1H), 7.15 (t, 1H), 4.78 (m, 1H), 2.5-2.1 (br, 13H), 2.17 (s, 3H), 1.91 (s, 10 6H), 1.68 (m, 2H), 1.58 (m, 2H),

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.80 min.

MS: MH⁺ 524.

Intermediate A: 2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]benzaldehyde
15

A mixture of 2-(4-iodophenoxy)benzaldehyde (1.31 g, 4.03 mmol, 1 equiv), PdCl₂(dppf)₂ (0.092 g, 0.13 mmol, 0.03 equiv), diboronpinacol ester (1.23 g, 4.84 mmol, 1.2 equiv), and potassium acetate (1.19 g, 12.1 mmol, 3.0 equiv) in DMF (15 mL) was heated at 80 °C for 5.5 h. The reaction mixture was allowed to cool to
20 ambient temperature and the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (50 mL) and the resulting solid was removed by filtration through a pad of Celite with the aid of CH₂Cl₂ (100 mL) and Et₂O (100 mL). The filtrate was concentrated to afford a brown oil which was purified by column chromatography on silica gel (elution with 500 mL of 5% MeOH/CH₂Cl₂) to
25 afford 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]benzaldehyde as a red-brown oil (0.875 g, 2.70 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 10.30 (1H, s), 7.87-7.89 (1H, m), 7.69-7.75 (3H, m), 7.36-7.38 (1H, m), 7.05-7.22 (3H, m), and 1.29 (12H, s).

30 **Example 270** 2-[4-(4-Amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenoxy]acetamide

A mixture of 4-(4-amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-

yl)phenol (0.050 g, 0.17 mmol, 1.0 equiv), dioxane (1.7 mL), and sodium hydride (60%, 0.010 g, 0.17 mmol, 1.0 equiv) was stirred at ambient temperature for 10 minutes. Iodoacetamine (0.031 g, 0.17 mmol, 1.0 equiv) was added. The reaction mixture was stirred at ambient temperature for 30 minutes and then heated at 110 °C for 3.5 h. The mixture was allowed to cool to ambient temperature and the resulting solid was removed by filtration with the aid of CH₂Cl₂ (5 mL) and EtOAc (5 mL). The solvent was removed under reduced pressure to afford a yellow solid which was triturated from EtOAc to afford 2-[(4-amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)oxy]acetamide as a beige solid (0.045 g, 0.13 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 8.22 (1H, s), 7.60 (2H, d), 7.12 (2H, d), 5.20-5.25 (1H, m), 4.50 (2H, s), 2.02-2.10 (4H, m), 1.87-1.90 (2H, m), 1.68-1.71 (2H, m); RP-HPLC (Delta Pak C18, 5μm, 300 Å Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 12.38 min. MS: MH⁺ 353.

Example 271 Methyl 5-[4-(4-amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenoxy]-2-furoate

A mixture of 4-(4-amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenol (0.107 g, 0.362 mmol, 1.0 equiv), DMSO (0.5 mL), sodium hydride (60%, 0.030 g, 0.72 mmol, 2.0 equiv), and methyl-5-nitro-2-furoate (0.062 g, 0.36 mmol, 1.0 equiv) was heated at 90 °C for 3 h. The reaction mixture was allowed to cool to room temperature, poured into ice water (10 mL), and extracted with three portions of CH₂Cl₂ (50 mL each). The combined organic extracts were washed with 5% aqueous KOH (50 mL) and the organic layer was dried over MgSO₄, filtered, and concentrated to afford a red oil which was purified by column chromatography on silica gel (elution with 300 mL of 5% MeOH/CH₂Cl₂) to afford methyl 5-[4-(4-amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenoxy]-2-furoate as a red solid (0.070 g, 0.17 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 8.24 (1H, s), 7.70-7.74 (2H, m), 7.35-7.39 (3H, m), 6.9 (2H, bs), 6.02 (1H, s), 5.22-5.26 (1H, m), 3.79 (3H, s), 2.01-2.11 (4H, m), 1.88-1.91 (2H, m), 1.67-1.71 (2H, m). RP-HPLC (Delta Pak C18, 5μm, 300 Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 18.17 min. MS: MH⁺ 420.

Example 272 5-[4-(4-Amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenoxy]-2-furoic acid

A mixture of methyl 5-[4-(4-amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenoxy]-2-furoate (0.030 g, 0.072 mmol, 1 equiv) and sodium hydroxide (0.020 g, 0.50 mmol, 7 equiv) in 50% EtOH:water (1 mL) was heated at 80 °C for 6 h. The reaction mixture was allowed to cool to ambient temperature and diluted with water (10 mL). The mixture was neutralized by the addition of 1 M HCl and extracted with two portions of CH₂Cl₂ (20 mL each) and two portions of EtOAc (20 mL each). The combined organic extracts were dried over MgSO₄, filtered, and concentrated to afford a yellow oil which was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 Å, 25 cm; 50%-100% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give a light brown solid (0.009 g, 0.022 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 13.0 (1H, bs), 8.23 (1H, s), 7.74 (2H, d), 7.35 (2H, d), 7.29 (1H, s), 6.03 (1H, s), 5.21-5.28 (1H, m), 2.01-2.11 (4H, m), 1.89-1.90 (2H, m), 1.68-1.71 (2H, m). RP-HPLC (Hypercil C18, 5µm, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1M ammonium acetate over 15 min, 1mL/min) R_t 6.45 min. MS: MH⁺ 406.

Example 273 1-Cyclopentyl-3-[4-(3-thienyloxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of 4-(4-amino-1-cyclopentyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenol (0.212 g, 0.718 mmol, 1 equiv), potassium carbonate (0.060 g, 0.43 mmol, 0.6 equiv), copper powder (0.015 g, 0.24 mmol, 0.33 equiv), and 3-bromothiophene (0.09 mL, 0.9 mmol, 1.3 equiv) in DMF (7.2 mL) was heated at 153 °C for 24 hr. The reaction mixture was allowed to cool to ambient temperature, concentrated, and the residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 Å, 25 cm; 10%-60% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give 1-cyclopentyl-3-[4-(3-thienyloxy)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a light brown solid (0.060 g, 0.16 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 9.77 (1H, s), 8.46 (1H, s), 8.41 (1H, s), 7.73-7.74 (1H, m), 7.57 (2H, d, *J* = 4.5 Hz), 7.46-

7.48 (1H, m), 7.15 (1H, d, $J = 5.2$ Hz), 6.96 (2H, d, $J = 8.6$ Hz), 5.24-5.30 (1H, m), 2.03-2.05 (4H, m), 1.89-1.93 (2H, m), 1.70-1.72 (2H, m). RP-HPLC (Delta Pak C18, 5 μ m, 300 Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 18.76 min. MS: MH^+ 378.

5 Example 274 Cis-3-{3-[(benzo[*b*]furan-2-ylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monoacetate salt

A mixture of cis-3-(3-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.107 g, 0.263 mmol, 1 equiv), glacial acetic acid (0.06 mL, 1.0 mmol, 3.8 equiv), benzo[B]furan-2-carboxaldehyde (0.1 g, 0.3 mmol, 1 equiv), sodium triacetoxymethylborohydride (0.212 g, 1.0 mmol, 3.8 equiv), and dichloroethane (2 mL) was stirred at ambient temperature for 4.5 h. Aqueous sodium bicarbonate was added, the organic layer was separated, and the aqueous layer was extracted with two portions of CH₂Cl₂ (10 mL each). The combined organic extracts were dried over MgSO₄, filtered, and concentrated to afford a yellow oil which was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 10%-60% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give cis-3-{3-[(benzo[*b*]furan-2-ylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monoacetate salt as a white solid (0.017 g, 0.031 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δ H 8.22 (1H, s), 7.51-7.58 (2H, m), 7.22-7.28 (3H, m), 6.98 (1H, s), 6.79-6.84 (2H, m), 6.59-6.62 (1H, m), 4.76-4.81 (1H, m), 4.50 (2H, d, $J = 5.6$ Hz), 2.19-2.24 (14H, m), 2.05-2.07 (2H, m), 1.91 (3H, s), 1.60-1.75 (4H, m); RP-HPLC (Delta Pak C18, 5 μ m, 300 Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 13.99 min. MS: MH^+ 537.

Example 275 Cis-3-{3-[di(2-furylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

30 A mixture of cis-3-(3-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.120 g, 0.296 mmol, 1 equiv), furfural (0.03 mL, 0.3 mmol, 1.1 equiv), glacial acetic acid (0.07 mL, 1.1 mmol, 3.8 equiv), and

sodium triacetoxyborohydride (0.314 g, 1.48 mmol, 5.0 equiv) in dichloroethane (2 mL) was stirred at ambient temperature for 60 h. Saturated aqueous sodium bicarbonate solution (5 mL) was added, the organic layer was separated, and the aqueous layer was extracted with two portions of CH₂Cl₂ (10 mL each). The organic
5 extracts were dried over MgSO₄, filtered, and concentrated to afford a yellow oil. Purification by column chromatography on silica gel (elution with 200 mL of 5% MeOH/ CH₂Cl₂, 100 mL of 10% MeOH/ CH₂Cl₂, and 300 mL of 10:20:70% MeOH/Et₃N/ CH₂Cl₂) afforded cis-3-{3-[di(2-furylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a white
10 solid (0.051 g, 0.10 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 8.22 (1H, s), 7.60 (2H, s), 7.31-7.35 (1H, m), 7.19 (1H, s), 7.00 (1H, d, *J* = 8.4 Hz), 6.93 (1H, d, *J* = 7.6 Hz), 6.39 (2H, s), 6.32 (2H, s), 4.77-4.80 (1H, m), 4.60 (4H, s), 2.23-2.39 (11H, m), 2.16 (3H, s), 2.05-2.07 (2H, m), 1.59-1.71 (4H, m); RP-HPLC (Delta Pak C18, 5μm, 300 Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1
15 mL/min) R_t 14.52 min. MS: MH⁺ 567.

Example 276 Cis-*N*-[2-(3-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzyl]trifluoromethanesulfonamide diacetate salt

20 To a mixture of cis-3-4-[2-(aminomethyl)phenoxy]phenyl-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.018 g, 0.035 mmol, 1 equiv) and pyridine (0.4 mL) at 0 °C was added CF₃SO₂Cl (0.05 mL, 0.04 mmol, 1.2 equiv) dropwise over 20 sec. The reaction mixture was allowed to warm slowly to ambient temperature and stirred for 3 h. The solvent was evaporated under
25 reduced pressure and the oily yellow residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 Å, 25 cm; 10%-60% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give cis-*N*-[2-(3-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-
30 yl}phenoxy)benzyl]trifluoromethanesulfonamide diacetate salt (0.004 g, 0.006 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 8.22 (1H, s), 7.61-7.67 (3H, m), 7.25-7.30 (2H, m), 7.19-7.23 (2H, m), 6.96-6.98 (1H, m), 4.77-4.81 (1H, m), 4.25 (2H, s),

2.09-2.54 (14H, m), 2.05-2.08 (2H, m), 1.91 (6H, s), 1.57-1.74 (4H, m); RP-HPLC (Delta Pak C18, 5 μ m, 300 Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 15.15 min. MS: MH⁺ 645.

5 Example 277 Cis-2-(3-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzaldehyde

A mixture of cis-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.970 g, 2.20 mmol, 1 equiv), 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]benzaldehyde (0.842 g, 2.60 mmol, 10 1.2 equiv), tetrakis(triphenylphosphine)palladium (0.186 g, 0.180 mmol, 0.08 equiv), DME (9 mL), and sodium carbonate monohydrate (0.655 g, 5.30 mmol, 2.4 equiv) in water (7 mL) was heated at 85 °C for 7 h then allowed to cool to ambient temperature. Saturated aqueous sodium bicarbonate solution (50 mL) was added, and the solution was extracted with EtOAc (25 mL). The organic extract was dried 15 over MgSO₄, filtered, and concentrated to afford a light brown solid. Trituration from Et₂O (35 mL) afforded cis-2-(3-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzaldehyde as an off-white solid (0.830 g, 1.62 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δH 10.42 (1H, s), 8.24 (1H, s), 7.89 (1H, d, *J* = 7.7 Hz), 7.69-7.71 (3H, m), 7.30-7.36 (1H, m), 7.29 (2H, d, *J* = 6.3 Hz), 7.16 (1H, d, *J* = 8.2 Hz), 20 4.79-4.81 (1H, m), 2.18-2.55 (11H, m), 2.17 (3H, s), 2.05-2.09 (2H, m), 1.56-1.71 (4H, m); RP-HPLC (Delta Pak C18, 5 μ m, 300 Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 12.56 min. MS: MH⁺ 512.

25 Example 278 Cis-3-{3-[2-(1*H*-2-imidazolyl)phenoxy]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of cis-2-(3-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenoxy)benzaldehyde (0.102 g, 0.199 mmol, 1 equiv), glyoxal (0.12 mL, 0.99 mmol, 5 equiv), and ammonium carbonate (0.078 g, 30 0.99 mmol, 5 equiv) in methanol (1 mL) was stirred at ambient temperature for 16 h. Additional glyoxal (0.20 mL, 1.6 mmol, 8.3 equiv) and ammonium carbonate (0.130 g, 1.66 mmol, 8.4 equiv) were added and the reaction mixture was stirred at

ambient temperature for 24 h. The crude reaction mixture was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 10%-60% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give cis-3-{3-[2-(1*H*-2-imidazolyl)phenoxy]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a brown solid (0.010 g, 0.018 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δ H 8.23 (1H, s), 8.11-8.13 (1H, dd, *J* = 7.7, 1.9 Hz), 7.95 (1H, s), 7.66 (2H, d, *J* = 8.5 Hz), 7.34-7.39 (1H, m), 7.23-7.27 (3H, m), 7.07-7.19 (3H, m), 4.77-4.82 (1H, m), 2.16-2.56 (11H, m), 2.14 (3H, s), 2.05-2.11 (2H, m), 1.55-1.71 (4H, m); RP-HPLC (Delta Pak C18, 5 μ m, 300 Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 10.43 min. MS: MH⁺ 550.

Example 279 Cis-*N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-anilinoacetamide

A mixture of 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.151 g, 0.356 mmol, 1 equiv), potassium carbonate (0.098 g, 0.711 mmol, 2 equiv), and chloroacetylchloride (0.04 mL, 0.5 mmol, 1.5 equiv) in DMF (1.5 mL) was stirred at ambient temperature for 20 minutes and then aniline (0.32 mL, 3.5 mmol, 10 equiv) was added. The reaction mixture was stirred at ambient temperature for 72 h. The solvent was removed under reduced pressure and the residue was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 10%-60% acetonitrile - 0.1M ammonium acetate over 20 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was washed with saturated aqueous sodium bicarbonate (10 mL) and then extracted with CH₂Cl₂ (25 mL). The organic extract was dried over MgSO₄, filtered, and concentrated to give cis-*N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-anilinoacetamide as a yellow solid (0.010 g, 0.017 mmol): ¹H NMR (d₆ DMSO, 400 MHz): δ H 9.30 (1H, s), 8.35-8.38 (1H, m), 8.21 (1H, s), 7.21-7.23 (2H, m), 7.12-7.16 (2H, m), 6.64-6.66 (3H, m), 6.31-6.34 (1H, m), 4.77-

4.81 (1H, m), 3.90 (2H, d, $J = 6.0$ Hz), 3.82 (3H, s), 2.21-2.51 (11H, m), 2.16 (3H, s), 2.06-2.08 (2H, m), 1.55-1.70 (4H, m); RP-HPLC (Delta Pak C18, 5 μ m, 300 Å, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1 mL/min) R_t 12.37 min. MS: MH^+ 570.

5 Example 280 (2*S*)-3-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}propane-1,2-diol

To a solution of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol) was added (*R*)-(+)-glycidol (0.05 M in isopropanol, 2.8 mL, 0.00014 mol) at room temperature under an atmosphere of nitrogen. The mixture was stirred at 80 °C for three hours. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using ammonium hydroxide/methanol/dichloromethane (2:7:91) followed by ammonium hydroxide/methanol/dichloromethane (2:10:88) as mobile phase to yield (2*S*)-3-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}propane-1,2-diol (0.023 g, 0.000053 mol).

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.31 (s, 1H), 7.64 (d, 2H), 7.38 (m, 2H), 7.15 (m, 5H), 5.90 (br, 2H), 5.60 (m, 1H), 3.97 (m, 3H), 3.88 (m, 1H), 3.75 (m, 2H), 3.61 (m, 1H), 2.80 (m, 2H).

20 RP-HPLC (Hypersil C18, 5 μ m, 250 x 4.6 mm; 25% - 100% over 10 min with 0.1 M ammonium acetate, 1mL/min) R_t 8.6 min.

MS: MH^+ 433

Example 281 (2*R*)-3-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}propane-1,2-diol

25 The experimental procedure is similar to the synthesis of (2*S*)-3-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylpropane-1,2-diol using (*S*)-(-)-glycidol

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.36 (s, 1H), 7.67 (d, 2H), 7.39 (m, 2H), 7.15 (m, 5H), 5.65 (br, 3H), 4.00 (m, 3H), 3.90 (m, 1H), 3.75 (m, 2H), 3.62 (m, 1H), 2.85 (m, 2H).

30

RP-HPLC (Hypersil C18, 5 μ m, 250 x 4.6 mm; 25% - 100% over 10 min with 0.1 M ammonium acetate, 1mL/min) R_t 8.76 min.

MS: MH^+ 433

- 5 Example 282 *Tert*-butyl 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-4-hydroxy-1-piperidinecarboxylate

a) *Tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

- 10 A mixture of trimethylsulfoxonium iodide (2.62 g, 0.012 mol) and sodium hydride (0.44 g, 0.011 mol) in anhydrous dimethylsulfoxide (30 mL) was stirred at room temperature under an atmosphere of nitrogen for thirty minutes. The reaction mixture was cooled to 10 °C and *tert*-butyl 4-oxo-1-piperidinecarboxylate (2.0 g, 0.010 mol) in anhydrous dimethylsulfoxide (10 mL) was added. The reaction mixture was warmed to room temperature and stirred for one and a half hours. The mixture was poured into an aqueous saturated ammonium chloride solution (60 mL). The water phase was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with water (1 x 60 mL) and brine (1 x 50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to yield *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (2.12 g, 0.0099 mol).
- 15 1H NMR (Chloroform-*d*, 400 MHz) δ 3.74 (br, 2H), 3.44 (m, 2H), 2.69 (s, 2H), 1.80 (m, 2H), 1.47 (s, 9H), 1.46 (m, 2H)
- 20 TLC (ethyl acetate / dichloromethane = 20 : 80) R_f 0.57
- Tert*-butyl 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-4-hydroxy-1-piperidinecarboxylate

- 25 To a mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.4 g, 0.0011 mol) in isopropanol (40 mL) was added *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (0.27 g, 0.0013 mol) at room temperature under an atmosphere of nitrogen. The mixture was stirred at 80 °C for three and a half hours. Additional *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (0.13 g, 0.00061 mol) was added and the mixture was stirred at 80 °C for
- 30 seven hours. Furthermore, *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (0.13 g, 0.00061 mol) was added and the mixture was stirred at 60 °C for 18 hours,

then 80 °C for eight hours. The solvent was removed under reduced pressure. The residue was suspended in water (50 mL) and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (1 x 50 mL) and brine (1 x 50 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using methanol/dichloromethane (5:95) followed by methanol/dichloromethane (10:90) as mobile phase to yield *tert*-butyl 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-4-hydroxy-1-piperidinecarboxylate (0.243 g, 0.000425 mol).

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.38 (s, 1H), 7.67 (d, 2H), 7.43 (t, 2H), 7.17 (m, 3H), 7.10 (d, 2H), 5.78(m, 1H), 5.48 (br, 2H), 4.34 (br, 2H), 4.20 (br, 2H), 3.89 (br, 2H), 3.18 (br, 2H), 2.91 (br, 2H), 1.60 (br, 2H), (s, 9H).
RP-HPLC (Hypersil C18, 5 μ m, 250 x 4.6 mm; 25% - 100% over 10 min with 0.1 M ammonium acetate, 1mL/min) R_t 10.7 min.

MS: MH⁺ 572

Example 283 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-4-piperidinol

To a solution of *tert*-butyl 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-4-hydroxy-1-piperidinecarboxylate (0.090 g, 0.00016 mol) in dichloromethane (2 mL) was slowly added a 20 % solution of trifluoroacetic acid in dichloromethane (10 mL) at 0 °C under an atmosphere of nitrogen. The mixture was warmed to room temperature and stirred for four hours. The solvent was removed under reduced pressure. An aqueous solution of 5 N sodium hydroxide was added to pH 11 at 0 °C. The water phase was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with water (1 x 60 mL) and brine (1 x 60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to yield 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-4-piperidinol (0.045 g, 0.000096 mol).

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.37 (s, 1H), 7.68 (d, 2H), 7.42 (t, 2H), 7.11(m, 3H), 7.00 (d, 2H), 5.64(m, 1H), 5.43 (br, 2H), 4.02 (m, 4H), 3.28 (br, 1H),

3.10 (m, 4H), 2.67 (s, 2H), 1.67 (m, 4H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.5 min.

MS: MH⁺ 472

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Example 284 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-1-methyl-4-piperidinol

A mixture of 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-4-piperidinol (0.035 g, 0.000074 mol) and
10 formaldehyde (0.006 mL, 37 % in water, 0.000082 mol) in dichloroethane (4 mL) was stirred at room temperature under an atmosphere of nitrogen for one hr. Sodium triacetoxyborohydride (0.022 g, 0.000104 mol) was added into the mixture and stirred at ambient temperature under an atmosphere of nitrogen for eighteen hours. Molecular sieves (0.05 g, 3A, 4-8 mesh) and additional formaldehyde (0.006 mL, 37
15 % in water, 0.000082 mol) was added and the reaction mixture was stirred at room temperature for eighteen hours. The solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersil HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 25 min with 0.1 M ammonium acetate, 21mL/min) to yield 4-(3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanylmethyl)-
20 1-methyl-4-piperidinol (0.020 g, 0.000041 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.63 (s, 1H), 7.69 (d, 2H), 7.42 (t, 2H), 7.17 (m, 5H), 5.42 (m, 1H), 3.88 (m, 2H), 3.67 (m, 2H), 2.37 (m, 2H), 2.25 (m, 2H), 2.14 (s, 3H), 1.90 (s, 2H), 1.50 (m, 4H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M
25 ammonium acetate over 10 min, 1mL/min) Rt 8.5 min.

MS: MH⁺ 486

General Procedure:

A mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.06 g, 0.00017 mol, 1 eq.), the corresponding
30 chloroacetamide (0.0005 mol, 3 eq.), and *N,N*-diisopropylethylamine (0.033 g, 0.00026 mol, 1.5 eq.) in acetonitrile (2.5 mL) was stirred at 75 °C under an atmosphere of nitrogen for three hours. The mixture was poured into water (10 mL),

and the water phase was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL) and brine (1 x 10 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5%
5 - 100% over 25 min with 0.1 M ammonium acetate, 21mL/min) to yield the corresponding amide.

Example 285 *N*-methyl-2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-1-yl]-1-azetanyl}acetamide

10 a) Chloroacetamide: *N*-methyl-2-chloroacetamide

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.35 (s, 1H), 7.67 (d, 2H), 7.42 (m, 2H), 7.18 (m, 3H), 7.08 (d, 2H), 5.80 (br, 2H), 5.60 (m, 1H), 4.00 (m, 4H), 3.37 (s, 2H), 2.85 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

15 ammonium acetate over 10 min, 1mL/min) Rt 9.2 min.

MS: MH⁺ 430

Example 286 *N,N*-dimethyl-2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-1-yl]-1-azetanyl}acetamide

20 b) Chloroacetamide: *N,N*-dimethyl-2-chloroacetamide

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.33 (s, 1H), 7.65 (d, 2H), 7.41 (m, 2H), 7.16 (m, 3H), 7.08 (d, 2H), 5.86 (br, 2H), 5.67 (m, 1H), 4.15 (m, 2H), 3.90 (m, 2H), 3.57 (s, 2H), 3.00 (s, 3H), 2.90 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

25 ammonium acetate over 10 min, 1mL/min) Rt 9.3 min.

MS: MH⁺ 444

Example 287 *N*-isopropyl-2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-1-yl]-1-azetanyl}acetamide

30 c) Chloroacetamide: *N*-isopropyl-2-chloroacetamide

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.36 (s, 1H), 7.67 (d, 2H), 7.40 (m, 2H), 7.18 (m, 3H), 7.09 (d, 2H), 6.90 (br, 1H), 5.66 (m, 3H), 4.11 (m, 1H), 3.99 (m, 4H), 3.39

(s, 2H), 1.19 (d, 6H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.8 min.

MS: MH⁺ 458

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Example 288 *N*-(3-hydroxypropyl)-2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}acetamide

d) Chloroacetamide: *N*-(3-hydroxypropyl)-2-chloroacetamide

10 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.31 (s, 1H), 7.67 (d, 2H), 7.40 (m, 2H), 7.18 (m, 3H), 7.10 (d, 2H), 5.99 (br, 2H), 5.62 (m, 1H), 3.95 (m, 4H), 3.78 (m, 2H), 3.63 (m, 2H), 3.40 (s, 2H), 1.71 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.9 min.

15 MS: MH⁺ 474

Example 289 Ethyl 2-[(2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}acetyl)amino]acetate (4037150)

e) Chloroacetamide: ethyl 2-[(2-chloroacetyl)amino]acetate

20 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.37 (s, 1H), 7.66 (d, 2H), 7.65 (br, 1H), 7.40 (m, 2H), 7.18 (m, 3H), 7.09 (d, 2H), 5.67 (m, 1H), 5.56 (br, 2H), 4.23 (m, 2H), 4.10 (m, 4H), 4.00 (m, 2H), 3.47 (s, 2H), 1.29 (t, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.9 min.

25 MS: MH⁺ 502

Example 290 *N*-benzyl-2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}acetamide

f) Chloroacetamide: *N*-benzyl-2-chloroacetamide

30 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.25 (s, 1H), 7.63 (d, 2H), 7.40 (m, 2H), 7.33 (m, 5H), 7.16 (m, 5H), 5.72 (m, 1H), 4.49 (d, 2H), 3.97 (m, 4H), 3.44 (s, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 10 min, 1mL/min) Rt 10.7 min.

MS: MH^+ 506

5 Example 291 *N,N*-methoxymethyl-2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}acetamide

g) Chloroacetamide: *N,N*-methoxymethyl-2-chloroacetamide

1H NMR (Chloroform-*d*, 400 MHz) δ 8.37 (s, 1H), 7.67 (d, 2H), 7.42 (m, 2H), 7.18 (m, 3H), 7.08 (d, 2H), 5.71 (m, 1H), 5.48 (br, 2H), 4.16 (m, 2H), 3.92 (m, 2H), 3.72 (s, 3H), 3.69 (s, 2H), 3.18 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.5 min.

MS: MH^+ 460

15 Example 292 2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-1-morpholino-1-ethanone

h) Chloroacetamide: 2-chloro-1-morpholino-1-ethanone

1H NMR (Chloroform-*d*, 400 MHz) δ 8.36 (s, 1H), 7.67 (d, 2H), 7.42 (m, 2H), 7.18 (m, 3H), 7.08 (d, 2H), 5.71 (m, 3H), 4.13 (m, 2H), 3.93 (m, 2H), 3.69 (br, 4H), 3.60 (br, 4H), 3.51 (s, 2H).

20 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.3 min.

MS: MH^+ 486

25 Example 293 *N*-(3-methyl-5-isoxazolyl)-2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}acetamide

i) Chloroacetamide: *N*-(3-methyl-5-isoxazolyl)-2-chloroacetamide

1H NMR (Chloroform-*d*, 400 MHz) δ 10.10 (br, 1H), 8.37 (s, 1H), 7.66 (d, 2H), 7.40 (m, 2H), 7.19 (m, 3H), 7.09 (d, 2H), 6.26 (s, 1H), 5.65 (m, 1H), 4.07 (m, 4H), 3.54 (s, 2H), 2.28 (s, 3H).

30 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.3 min.

MS: MH⁺ 497

Example 294 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(1*H*-4-imidazolyl)-1-ethanone

A mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol), sodium 2-(1*H*-4-imidazolyl)acetate (0.0026 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0034 g, 0.000175 mol), *N, N*-diisopropylethylamine (0.033 g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous *N, N*-dimethylformamide (6 mL) was stirred for eighteen hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8μm, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(1*H*-4-imidazolyl)-1-ethanone (0.018 g, 0.00004 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.90 (br, 1H), 8.27 (s, 1H), 7.71 (d, 2H), 7.53 (s, 1H), 7.42 (m, 2H), 7.19 (m, 5H), 6.92 (br, 1H), 5.73 (m, 1H), 4.74 (m, 1H), 4.61 (m, 1H), 4.42 (m, 2H), 3.42 (s, 2H).

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.0 min.

MS: MH⁺ 467

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Example 295 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-(1*H*-4-imidazolyl)-1-propanone

A mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.10 g, 0.00028 mol), 3-(1*H*-4-imidazolyl)propanoic acid (0.050 g, 0.00035 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0068 g, 0.00035 mol), *N, N*-diisopropylethylamine (0.068 g, 0.00053 mol) and 1-hydroxy-7-azabenzotriazole (0.038 g, 0.00028 mol) in

30

anhydrous *N,N*-dimethylformamide (13 mL) was stirred for eighteen hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC

5 (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-(1*H*-4-imidazolyl)-1-propanone (0.040 g, 0.00008 mol).

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.96 (s, 1H), 7.77 (br, 1H), 7.64 (d, 2H), 7.40 (m, 2H), 7.17 (m, 3H), 7.08 (m, 2H), 6.90 (br, 1H), 5.78 (m, 1H), 5.56 (br, 2H), 4.76 (m, 1H), 4.57 (m, 3H), 2.98 (m, 2H), 2.55 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.0 min.

MS: MH⁺ 481

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General procedure

To a mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol, 1 eq.) and potassium carbonate (0.039 g, 0.00028 mol, 2 eq.) in anhydrous *N,N*-dimethylformamide was added
20 chloroacetylchloride (0.031 g, 0.00028 mol, 2 eq.) at room temperature. The mixture was stirred for ten minutes before the amine (0.0014 mol, 10 eq.) was added. The mixture was stirred at room temperature from one and a half hours to two days depending on the amine. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with
25 water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield the corresponding acetamides.

30 Example 296 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(2-hydroxyethyl)amino]-1-ethanone

a) Amine: 2-amino-1-ethanol

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.37 (s, 1H), 7.67 (d, 2H), 7.41 (m, 2H), 7.15 (m, 3H), 7.08 (m, 2H), 5.83 (m, 1H), 5.57 (br, 2H), 4.82 (m, 1H), 4.65 (m, 3H), 3.71 (m, 2H), 3.45 (m, 2H), 2.92 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

5 ammonium acetate over 10 min, 1mL/min) Rt 8.7 min.

MS: MH⁺ 460

Example 297 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(2-methoxyethyl)amino]-1-ethanone

10 b) Amine: 2-methoxy-1-ethanamine

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.38 (s, 1H), 7.67 (d, 2H), 7.41 (m, 2H), 7.18 (m, 3H), 7.10 (m, 2H), 5.83 (m, 1H), 5.54 (br, 2H), 4.81 (m, 1H), 4.64 (m, 2H), 4.56 (m, 1H), 3.55 (t, 2H), 3.41 (s, 2H), 3.37 (s, 3H), 2.88 (t, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

15 ammonium acetate over 10 min, 1mL/min) Rt 9.0 min. MS: MH⁺ 474

Example 298 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(3-hydroxypropyl)amino]-1-ethanone

c) Amine: 3-amino-1-propanol

20 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.37 (s, 1H), 7.67 (d, 2H), 7.41 (m, 2H), 7.18 (m, 3H), 7.10 (m, 2H), 5.86 (m, 1H), 5.54 (br, 2H), 4.81 (m, 1H), 4.64 (m, 3H), 3.87 (m, 2H), 3.48 (m, 2H), 3.01 (m, 2H), 1.83 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 10 min, 1mL/min) Rt 8.7 min.

25 MS: MH⁺ 474

Example 299 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(2,3-dihydroxypropyl)amino]-1-ethanone

d) Amine: 3-amino-1,2-propanediol

30 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.27 (s, 1H), 7.72 (d, 2H), 7.46 (m, 2H), 7.16 (m, 5H), 5.73 (m, 1H), 4.67 (m, 1H), 4.59 (m, 2H), 4.37 (m, 2H), 3.53 (m, 1H), 3.30 (m, 1H), 3.22 (m, 2H), 2.59 (m, 1H), 2.45 (m, 1H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.6 min.

MS: MH⁺ 490

- 5 Example 300 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(tetrahydro-2-furanylmethyl)amino]-1-ethanone

e) Amine: tetrahydro-2-furanylmethanamine

- 10 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.38 (s, 1H), 7.67 (d, 2H), 7.41 (m, 2H), 7.18 (m, 3H), 7.10 (m, 2H), 5.81 (m, 1H), 5.54 (br, 2H), 4.80 (m, 1H), 4.64 (m, 2H), 4.57 (m, 1H), 4.05 (m, 1H), 3.87 (m, 1H), 3.76 (m, 1H), 3.42 (m, 2H), 2.83 (m, 1H), 2.74 (m, 1H), 2.00 (m, 1H), 1.89 (m, 2H), 1.57 (m, 1H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.3 min.

- 15 MS: MH⁺ 500

Example 301 f) Amine: 2-piperidino-1-ethanamine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(2-piperidinoethyl)amino]-1-ethanone

- 20 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.27 (s, 1H), 7.70 (d, 2H), 7.42 (m, 2H), 7.18 (m, 5H), 5.73 (m, 1H), 4.60 (m, 2H), 4.36 (m, 2H), 3.24 (d, 2H), 2.60 (m, 2H), 2.36 (m, 6H), 1.49 (m, 4H), 1.36 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.4 min.

- 25 MS: MH⁺ 527

Example 302 g) Amine: *N,N,N*-trimethyl-1,2-ethanediamine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[[2-(dimethylamino)ethyl](methyl)amino]-1-ethanone

- 30 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.27 (s, 1H), 7.70 (d, 2H), 7.44 (m, 2H), 7.17 (m, 5H), 5.75 (m, 1H), 4.70 (m, 2H), 4.40 (m, 2H), 3.22 (d, 2H), 2.75 (br, 2H), 2.61 (m, 2H), 2.47 (s, 6H), 2.29 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.4 min.

MS: MH⁺ 501

5 Example 303

h) Amine: *N,N*-dimethyl-1,2-ethanediamine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-{[2-(dimethylamino)ethyl]amino}-1-ethanone acetate

10 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.33 (s, 1H), 7.67 (d, 2H), 7.42 (m, 2H), 7.15 (m, 3H), 7.11 (m, 2H), 5.81 (br, 3H), 4.81 (m, 1H), 4.59 (m, 3H), 3.38 (s, 2H), 2.89 (t, 2H), 2.68 (t, 2H), 2.43 (s, 6H), 2.05 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.0 min.

MS: MH⁺ 487

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Example 304

i) Amine: *N*-methyl- *N*-(1-methyl-4-piperidyl)amine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[methyl(1-methyl-4-piperidyl)amino]-1-ethanone

20 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.36 (s, 1H), 7.67 (d, 2H), 7.41 (m, 2H), 7.18 (m, 3H), 7.10 (m, 2H), 5.76 (m, 1H), 5.58 (br, 2H), 4.87 (m, 1H), 4.79 (m, 1H), 4.62 (m, 1H), 4.55 (m, 1H), 3.27 (m, 2H), 2.97 (br, 2H), 2.51 (br, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 2.04 (br, 2H), 1.79 (br, 2H), 1.65 (br, 2H).

25 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.1 min.

MS: MH⁺ 527

Example 305

j) Amine: 2-morpholino-1-ethanamine

30 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(2-morpholinoethyl)amino]-1-ethanone

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.38 (s, 1H), 7.67 (d, 2H), 7.40 (m, 2H), 7.19

(m, 3H), 7.09 (m, 2H), 5.86 (m, 1H), 5.50 (br, 2H), 4.82 (m, 1H), 4.67 (m, 3H), 3.77 (m, 4H), 3.50 (s, 2H), 2.92 (t, 2H), 2.66 (t, 2H), 2.57 (br, 4H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.1 min.

5 MS: MH⁺ 529

Example 306

k) Amine: 3-morpholino-1-propanamine

10 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[(3-morpholinopropyl)amino]-1-ethanone

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.38 (s, 1H), 7.68 (d, 2H), 7.41 (m, 2H), 7.18 (m, 3H), 7.10 (m, 2H), 5.85 (m, 1H), 5.54 (br, 2H), 4.81 (m, 1H), 4.64 (m, 3H), 3.74 (m, 4H), 3.40 (s, 2H), 2.83 (br, 2H), 2.52 (br, 6H), 1.80 (br, 2H).

15 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.9 min.

MS: MH⁺ 543

Example 307

l) Amine: 3-(1*H*-1-imidazolyl)-1-propanamine

20 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-{[3-(1*H*-1-imidazolyl)propyl]amino}-1-ethanone

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.37 (s, 1H), 7.65 (d, 2H), 7.40 (m, 3H), 7.15 (m, 3H), 7.08 (m, 3H), 6.93 (s, 1H), 5.82 (m, 1H), 5.62 (br, 2H), 4.75 (m, 1H), 4.62 (m, 3H), 4.07 (t, 2H), 3.27 (s, 2H), 2.58 (t, 2H), 1.97 (m, 2H).

25 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.7 min.

MS: MH⁺ 524

Example 308

30 m) Amine: 1-(3-aminopropyl)-2-pyrrolidinone

1-{3-[(2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-oxoethyl)amino]propyl}-2-pyrrolidinone

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.38 (s, 1H), 7.67 (d, 2H), 7.41 (m, 2H), 7.18 (m, 3H), 7.10 (m, 2H), 5.82 (m, 1H), 5.54 (br, 2H), 4.81 (m, 1H), 4.64 (m, 3H), 3.42 (m, 6H), 2.79 (t, 2H), 2.42 (t, 2H), 2.07 (m, 2H), 1.86 (br, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

5 ammonium acetate over 10 min, 1mL/min) Rt 9.0 min.

MS: MH⁺ 541

Example 309

n) Amine: 4-piperidinol

10 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(4-hydroxypiperidino)-1-ethanone

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.38 (s, 1H), 7.67 (d, 2H), 7.38 (m, 2H), 7.18 (m, 3H), 7.09 (m, 2H), 5.77 (m, 1H), 5.57 (br, 2H), 4.90 (m, 1H), 4.78 (m, 1H), 4.63 (m, 1H), 4.56 (m, 1H), 3.73 (br, 1H), 3.18 (s, 2H), 2.91 (br, 2H), 2.38 (br, 2H), 1.95 (br, 2H), 1.62 (br, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 10 min, 1mL/min) Rt 8.9 min.

MS: MH⁺ 500

20 Example 310

o) Amine: 4-piperidylmethanol

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[4-(hydroxymethyl)piperidino]-1-ethanone

25 ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.36 (s, 1H), 7.67 (d, 2H), 7.41 (m, 2H), 7.18 (m, 3H), 7.10 (m, 2H), 5.78 (m, 1H), 5.64 (br, 2H), 4.89 (m, 1H), 4.81 (m, 1H), 4.62 (m, 1H), 4.55 (m, 1H), 3.49 (m, 2H), 3.13 (s, 2H), 2.97 (m, 2H), 2.10 (m, 2H), 1.74 (m, 2H), 1.49 (br, 1H), 1.30 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 10 min, 1mL/min) Rt 9.0 min.

30 MS: MH⁺ 514

Example 311

p) Amine: 1-(2-methoxyethyl)piperazine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[4-(2-methoxyethyl)piperidino]-1-ethanone

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.26 (s, 1H), 7.71 (d, 2H), 7.42 (m, 2H), 7.18 (m, 5H), 5.69 (m, 1H), 4.73 (m, 2H), 4.38 (m, 2H), 3.39 (t, 2H), 3.30 (s, 2H), 3.21 (s, 3H), 3.05 (m, 2H), 2.43 (br, 8H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.0 min.

MS: MH⁺ 543

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Example 312

q) Amine: morpholine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-morpholino-1-ethanone

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.26 (s, 1H), 7.70 (d, 2H), 7.42 (m, 2H), 7.18 (m, 5H), 5.70 (m, 1H), 4.73 (m, 2H), 4.40 (m, 2H), 3.57 (m, 4H), 3.08 (m, 2H), 2.44 (m, 4H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.6 min.

20 MS: MH⁺ 486

Example 313

r) Amine: 1-methylpiperazine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(4-methylpiperazino)-1-ethanone

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.26 (s, 1H), 7.70 (d, 2H), 7.44 (m, 2H), 7.16 (m, 5H), 5.70 (m, 1H), 4.70 (m, 2H), 4.35 (m, 2H), 3.29 (s, 2H), 3.06 (m, 2H), 2.45 (br, 6H), 2.16 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.0 min.

30 MS: MH⁺ 499

Example 314

s) Amine: 4-piperidinopiperidine

1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-[4-(piperid-1-yl)piperidino]-1-ethanone

- 5 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.26 (s, 1H), 7.70 (d, 2H), 7.44 (m, 2H), 7.18 (m, 5H), 5.70 (m, 1H), 4.73 (m, 2H), 4.40 (m, 1H), 4.30 (m, 1H), 2.88 (m, 4H), 2.38 (br, 4H), 2.13 (m, 1H), 2.00 (m, 2H), 1.61 (br, 2H), 1.43 (br, 6H), 1.34 (br, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.2 min.

- 10 MS: MH⁺ 567

Example 315

t) Amine: 1*H*-imidazole

- 15 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(1*H*-1-imidazolyl)-1-ethanone

¹H NMR (Chloroform-*d*, 400 MHz) δ 8.31 (s, 1H), 7.87 (br, 1H), 7.65 (d, 2H), 7.41 (m, 2H), 7.18 (m, 4H), 7.10 (m, 3H), 5.90 (br, 2H), 5.80 (m, 1H), 4.82 (m, 1H), 4.72 (m, 3H), 4.59 (m, 1H), 4.47 (m, 1H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

- 20 ammonium acetate over 10 min, 1mL/min) Rt 9.2 min.

MS: MH⁺ 467

Example 316 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(methylamino)-1-ethanone acetate

- 25 A mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol), 2-[(*tert*-butoxycarbonyl)(methyl)amino] acetic acid (0.0033 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0034 g, 0.000175 mol), *N*, *N'*-diisopropylethylamine (0.033 g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous *N,N*-dimethylformamide (6 mL) was stirred for eighteen hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and
- 30

washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield *tert*-butyl *N*-(2-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-oxoethyl)-*N*-methylcarbamate. The solid was dissolved in dichloromethane (2 mL) and a 25 % solution of trifluoroacetic acid in dichloromethane (4 mL) was slowly added to the reaction at 0 °C. The reaction mixture was stirred for 5 hours at room temperature. The solvent was removed under reduced pressure. A 5 N aqueous solution of sodium hydroxide was added to pH 11 at 0 °C. The water phase was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with water (1 x 60 mL) and brine (1 x 60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to yield 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(dimethylamino)-1-ethanone acetate (0.022 g, 0.00004 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.27 (s, 1H), 7.69 (d, 2H), 7.42 (m, 2H), 7.15 (m, 5H), 5.75 (m, 1H), 4.70 (m, 1H), 4.60 (m, 1H), 4.40 (m, 1H), 4.35 (m, 1H), 3.18 (s, 2H), 2.25 (s, 3H), 1.90 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.9 min.

MS: MH⁺ 430

Example 317 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(dimethylamino)-1-ethanone acetate

A mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol), 2-(dimethylamino)acetic acid (0.0018 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0034 g, 0.000175 mol), *N*, *N*'-diisopropylethylamine (0.033 g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous *N,N*-dimethylformamide (6 mL) was stirred for eighteen hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS

C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-2-(dimethylamino)-1-ethanone acetate (0.022 g, 0.00004 mol).

- 5 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.27 (s, 1H), 7.69 (d, 2H), 7.42 (m, 2H), 7.15 (m, 5H), 5.69 (m, 1H), 4.70 (m, 2H), 4.40 (m, 2H), 2.97 (m, 2H), 2.20 (s, 6H), 1.89 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.6 min.

- 10 MS: MH⁺ 444

Example 318 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-(diethylamino)-1-propanone

- A mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol), 3-(diethylamino)propionic acid hydrochloride (0.0032 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0034 g, 0.000175 mol), *N*, *N*'-diisopropylethylamine (0.068 g, 0.00053 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous *N,N*-dimethylformamide (6 mL) was stirred for
- 15
- 20 18 hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{3-[4-amino-3-(4-
- 25 phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-(diethylamino)-1-propanone (0.025 g, 0.00005 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.26 (s, 1H), 7.69 (d, 2H), 7.44 (m, 2H), 7.14 (m, 5H), 5.70 (m, 1H), 4.67 (m, 2H), 4.37 (m, 2H), 2.66 (m, 2H), 2.45 (m, 4H), 2.21 (m, 2H), 0.95 (m, 6H).

- 30 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.3 min.

MS: MH⁺ 486

Example 319 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-(methylamino)-1-ethanone acetate

A mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.054 g, 0.00014 mol), 2-[(*tert*-butoxycarbonyl)(methyl)amino] acetic acid (0.0033 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0034 g, 0.000175 mol), *N*, *N*'-diisopropylethylamine (0.033 g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous *N*, *N*-dimethylformamide (6 mL) was stirred for eighteen hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield *tert*-butyl *N*-(2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-oxoethyl)-*N*-methylcarbamate. The solid was dissolved in dichloromethane (2 mL) and 25 % trifluoroacetic acid in dichloromethane (4 mL) was slowly added into the reaction at 0 °C. The reaction mixture was stirred for 5 hours at room temperature. The solvent was removed under reduced pressure. To the residue a 5 N aqueous solution of sodium hydroxide was added to pH 11 at 0 °C. The water phase was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with water (1 x 60 mL) and brine (1 x 60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to yield 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-(methylamino)-1-ethanone acetate (0.010 g, 0.00002 mol).
¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.25 (s, 1H), 7.67 (d, 2H), 7.45 (m, 2H), 7.13 (m, 5H), 4.94 (br, 1H), 4.53 (br, 1H), 3.99 (br, 1H), 3.36 (m, 2H), 3.21 (br, 1H), 2.85 (br, 1H), 2.26 (s, 3H), 2.10 (br, 1H), 1.96 (br, 3H), 1.85 (s, 3H).
RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.1 min.
MS: MH⁺ 458

Example 320 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-(dimethylamino)-1-ethanone

A mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.054 g, 0.00014 mol), 2-(dimethylamino)acetic acid (0.0018 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0034 g, 0.000175 mol), *N*, *N*'-diisopropylethylamine (0.033 g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous *N*, *N*-dimethylformamide (6 mL) was stirred for eighteen hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-(dimethylamino)-1-ethanone (0.031 g, 0.00007 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.25 (s, 1H), 7.67 (d, 2H), 7.42 (m, 2H), 7.15 (m, 5H), 4.97 (br, 1H), 4.50 (br, 1H), 4.22 (br, 1H), 3.25 (br, 1H), 3.12 (m, 2H), 2.83 (br, 1H), 2.21 (s, 6H), 2.16 (br, 1H), 1.90 (br, 3H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.3 min. MS: MH⁺ 472

Example 321 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-(diethylamino)-1-propanone acetate

A mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.054 g, 0.00014 mol), 3-(diethylamino)propionic acid hydrochloride (0.0032 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0034 g, 0.000175 mol), *N*, *N*'-diisopropylethylamine (0.068 g, 0.00053 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous *N*, *N*-dimethylformamide (6 mL) was stirred for eighteen hours at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was

purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-(diethylamino)-1-propanone acetate (0.038g, 0.00006 mol).

5 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.25 (s, 1H), 7.67 (d, 2H), 7.42 (m, 2H), 7.15 (m, 5H), 4.97 (br, 1H), 4.52 (br, 1H), 4.03 (br, 1H), 3.27 (br, 1H), 2.80 (br, 1H), 2.66 (m, 2H), 2.49 (m, 8H), 2.11 (br, 1H), 1.95 (br, 3H), 1.87 (s, 3H), 0.93 (m, 6H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.7 min.

10 MS: MH⁺ 514

General procedure

To a mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00013 mol, 1 eq.) and potassium carbonate (0.036 g, 0.00026 mol, 2 eq.) in anhydrous *N, N*-dimethylformamide (3 mL) was added
15 chloroacetylchloride (0.028 g, 0.00026 mol, 2 eq.) at room temperature. The mixture was stirred for ten min. before the amine (0.0013 mol, 10 eq.) was added. The mixture was stirred at room temperature from three hours. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced
20 pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield the corresponding acetamides.

Example 322 a) Amine: morpholine

25 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-morpholino-1-ethanone acetate

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.24 (s, 1H), 7.65 (d, 2H), 7.44 (m, 2H), 7.16 (m, 5H), 4.99 (m, 1H), 4.47 (br, 1H), 4.19 (br, 1H), 3.58 (m, 4H), 3.25 (m, 2H), 3.11 (m, 1H), 2.83 (br, 1H), 2.43 (m, 4H), 2.25 (br, 1H), 1.99 (br, 3H), 1.89 (s, 3H).

30 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.7 min.

MS: MH⁺ 514

Example 323 b) Amine: 1-methylpiperazine

1-{4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidino}-
2-(4-methylpiperazino)-1-ethanone acetate

5 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.24 (s, 1H), 7.65 (d, 2H), 7.44 (m, 2H), 7.16 (m, 5H), 4.99 (m, 1H), 4.47 (br, 1H), 4.19 (br, 1H), 3.29 (m, 2H), 3.22 (m, 2H), 3.05 (m, 1H), 2.80 (br, 1H), 2.33 (br, 6H), 2.22 (br, 1H), 2.13 (s, 3H), 1.94 (br, 3H), 1.89 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M
10 ammonium acetate over 10 min, 1mL/min) Rt 9.3 min.
MS: MH⁺ 527

Example 324 and Example 325 *Cis* and *trans* 2-{4-[4-amino-3-(4-
15 phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-
1-yl]-1-hydroxycyclohexyl}acetic acid

a) *Cis* and *trans tert*-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-
d]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetate

A suspension of acid washed zinc dust (0.350 g, 0.00535 mol) and cuprous
20 chloride (0.053 g, 0.000535 mol) in anhydrous tetrahydrofuran (10 mL) was heated
at reflux for thirty minutes. The heat was discontinued and a portion (1 mL) of a
solution of *tert*-butyl 2-bromoacetate (0.261 g, 0.00134 mol) in tetrahydrofuran (10
mL) was added immediately. The mixture was stirred five minutes, and then the
remainder of the mixture was added dropwise. The mixture was heated at reflux for
25 thirty minutes. The mixture was cooled to room temperature and a solution of 4-(4-
amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanone
(0.200 g, 0.00053 mol) in anhydrous tetrahydrofuran (5 mL) was added dropwise
over five minutes. The mixture was stirred at room temperature four hours. The
unreacted zinc was removed by filtration, washing with ether (3 x 5 mL). The filtrate
30 was washed with water (3 x 5 mL) and brine (10 mL). The organic layer was dried
over magnesium sulfate, and the solvent was removed *in vacuo*. The crude material
had a *cis:trans* ratio of 1:1. The isomers were separated by flash column
chromatography on silica using dichloromethane /methanol (98:2). The solvent was

removed *in vacuo* to give the less polar *trans tert*-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetate as a white solid (0.092 g, 0.00018 mol) and the more polar *cis tert*-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetate as a white solid (0.049 g, 0.000096 mol).

5 *Cis tert*-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.66 (d, 2H), 7.43 (t, 2H), 7.11-7.20 (m, 5H), 4.70-4.84 (m, 1H), 2.36 (s, 2H), 1.89-2.12 (m, 4H), 1.51-1.67 (m, 2H), 1.43 (s, 9H), 1.37-1.42 (m, 4H).

10 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 19.31 min.;

MS: MH⁺ 516.

Trans tert-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetate

15 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.66 (d, 2H), 7.43 (t, 2H), 7.11-7.20 (m, 5H), 4.45-4.61 (m, 1H), 2.36 (s, 2H), 1.78-1.85 (m, 2H), 1.64-1.71 (m, 2H), 1.43 (s, 9H), 1.36-1.45 (m, 4H) .

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 19.64 min.;

20 MS: MH⁺ 516.

Cis 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetic acid

Cis tert-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetate (0.092 g, 0.000178 mol) was reacted with a solution of 20% trifluoroacetic acid in dichloromethane (10 mL) at room temperature under a nitrogen atmosphere for forty-five minutes. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (25 mL) and washed with water (3 x 10 mL). The solution was dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was suspended in water (25 mL) and lyophilized to give *cis* 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetic acid as a white powder (0.078 g,

25

30

0.000170 mol).

^1H NMR (DMSO- d_6 , 400MHz) δ 8.32 (s, 1H), 7.66 (d, 2H), 7.44 (t, 2H), 7.11-7.22 (m, 5H), 4.62-4.67 (m, 1H), 2.39 (s, 2H), 2.27-2.43 (m, 2H), 1.55-1.90 (m, 6H).

RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile – 0.1M

5 ammonium acetate over 20 min, 1mL/min) R_t 13.65 min.

MS: MH^+ 460.

Trans 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetic acid

Trans tert-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-
10 *d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetate (0.049 g, 0.000096 mol) was reacted with a solution of 20% trifluoroacetic acid in dichloromethane (10 mL) at room temperature under a nitrogen atmosphere for forty-five minutes. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (25 mL) and washed with water (3 x 10 mL). The solution was dried over magnesium sulfate and the
15 solvent was removed *in vacuo*. The residue was suspended in water (25 mL) and lyophilized to give *trans* 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetic acid as a white powder (0.038 g, 0.000083 mol).

^1H NMR (DMSO- d_6 , 400MHz) δ 8.36 (s, 1H), 7.67 (d, 2H), 7.44 (t, 2H), 7.11-7.22
20 (m, 5H), 4.72-4.79 (m, 1H), 1.99 (s, 2H), 1.91-2.09 (m, 6H), 1.61-1.65 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.46 min.

MS: MH^+ 460.

25 Example 326 *Trans* 1-{3-[(benzyloxy)methyl]cyclobutyl}-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

^1H NMR (DMSO- d_6 , 400MHz) δ 8.23 (s, 1H), 7.69 (d, 2H), 7.44 (t, 2H), 7.37- 7.39 (m, 4H), 7.29-7.31 (m, 1H), 7.11-7.21 (m, 5H), 5.42-5.47 (m, 1H), 4.57 (s, 1H), 3.63 (d, 2H), 2.76-2.81 (m, 2H), 2.60-2.70 (m, 1H), 2.28-2.34 (m, 2H).

30 RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 21.92 min.

MS: MH^+ 478.

Example 327 [3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-(hydroxymethyl)cyclobutyl]methanol

a) Diethyl 3-[(methylsulfonyl)oxy]-1,1-cyclobutanedicarboxylate.

5 A solution of diethyl 3-hydroxy-1,1-cyclobutanedicarboxylate (0.268 g, 0.00116 mol) in pyridine (7 mL) was cooled to 0° C. Methanesulfonyl chloride (0.11 mL, 0.160 g, 0.00140 mol) was added dropwise, keeping the temperature below 2° C. The mixture was stirred for four hours, and then poured into ice water (20 mL) and extracted with ethyl ether (2 x 10 mL). The combined organic layers
10 were washed with water (3 x 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give diethyl 3-[(methylsulfonyl)oxy]-1,1-cyclobutanedicarboxylate (0.302 g, 0.00102 mol) as a yellow oil.:

¹H NMR (CDCl₃, 400MHz) 5.08-5.11 (m, 1 H), 4.23 (q, 4H), 3.01 (s, 3H), 2.98-
15 3.03 (m, 2H), 2.81-2.86 (m, 2H), 1.27 (t, 6H).

b) Diethyl 3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1,1-cyclobutanedicarboxylate

 A solution of 3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.129 g, 0.00042 mmol) in *N,N*-dimethylformamide (5 mL) was reacted with
20 diethyl 3-[(methylsulfonyl)oxy]-1,1-cyclobutanedicarboxylate (0.150 g, 0.00051 mmol) and cesium carbonate (0.166 g, 0.00051 mmol) at 70° C for five days. The reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate and the solvent was
25 removed *in vacuo*. The residue was purified by flash column chromatography on silica using dichloromethane/methanol (98:2). The solvent was removed *in vacuo* to give diethyl 3-[4-amino-3-(4-phenoxy-phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1,1-cyclobutanedicarboxylate (0.060g, 0.00012 mol) as a tan solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.24 (s, 1H), 7.67 (d, 2H), 7.44 (t, 2H), 7.12-7.21
30 (m, 5H), 5.38-5.42 (m, 1H), 4.16-4.28 (m, 4H), 3.14-3.17 (m, 2H), 2.96-3.00 (m, 2H), 1.17-1.28 (m, 6H).

c) [3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-

(hydroxymethyl)cyclobutyl]methanol

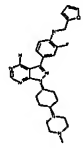
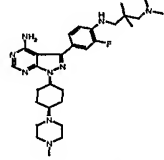
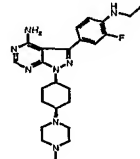
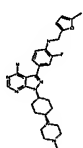
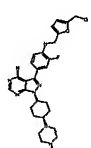
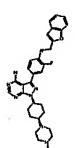
To a solution of diethyl 3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1,1-cyclobutanedicarboxylate (0.045 g, 0.000089 mol) in tetrahydrofuran (10 mL) lithium aluminum hydride (0.010 g, 0.000270 mol) was added. The reaction mixture was stirred six hours at ambient temperature, after which time water (1.0 mL) was added. The mixture was filtered through a pad of Celite ® 521. The solvent was removed from the filtrate *in vacuo*. The residue was partitioned between water (15 mL) and ethyl acetate (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 A, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to [3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-(hydroxymethyl)cyclobutyl]methanol as a white solid (0.007 g, 0.000017 mol):

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.22 (s, 1H), 7.68 (d, 2H), 7.44 (t, 2H), 7.11- 7.20 (m, 5H), 5.28-5.34 (m, 1H), 4.76 (t, 1 H), 4.58 (t, 1H), 3.55 (d, 2H) 3.47 (d, 2H), 2.46 –2.55 (m, 2H), 2.24-2.31 (m, 2H).

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.81 min.
MS: MH⁺ 418.

Examples 328- 334 General procedure for the synthesis of aryl alkyl cis-3-(4-Amino-3-fluorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine analogs.

These compounds were synthesized using the procedure previously described for the synthesis of aryl alkyl cis-3-(4-Amino-3-fluorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine analogs

329		505.3	12.05	
330		538.4	9.27	
331		453.2	11.16	
332		519.1	12.95	
333		535.3	10.57	
334		555.3	14.08	

Example 335 *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-5-chloro-2-thiophenesulfonamide maleate salt.

5

This compound was synthesized as the maleate salt using the procedure previously described for cis and trans-3-(4-Amino-3-fluorophenyl)-1-[4-(4-

methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

HPLC-RT: 12.39 min. (flow rate: 1 mL/min, λ = 254 nm Gradient: 5% to 85% acetonitrile/0.1M aqueous ammonium acetate gradient over 20 min.; Deltapak C18, 300Å, 5µm, 150 x 3.9 mm column); m/z (MH^+) = 606.1.

5

Example 336 1-(4-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}piperidino)-2-(dimethylamino)-1-ethanone.

a). *tert*-Butyl 4-hydroxy-1-piperidinecarboxylate

10 *tert*-Butyl 4-oxo-1-piperidinecarboxylate (20 g, 100.4 mmol) was dissolved in methanol (250 mL) then cooled to 0 °C and sodium borohydride (3.8 g, 100.4 mmol) was added over 10 min. The reaction mixture was warmed from 0 °C to room temperature. After 4 hours, the reaction was concentrated under reduced pressure and the remaining syrup was dissolved in 3:1 dichloromethane/isopropanol (400
15 mL). The organic layer was washed with aqueous 1N sodium hydroxide (200 mL). The aqueous layer was then extracted with 3:1 dichloromethane/isopropanol (3 x 150 mL). The organic layers were washed with brine (400 mL) then dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield *tert*-butyl 4-hydroxy-1-piperidinecarboxylate as a light yellow syrup (20 g, 100.4 mmol). ¹H
20 NMR (d_6 -DMSO): δ 1.21-1.28 (m, 2H), 1.38 (s, 9H), 1.65-1.69 (m, 2H), 2.94-2.96 (m, 2H), 3.59-3.68 (m, 3H), 4.68 (d, 1H).

b). *tert*-Butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate.

3-Iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (17.3 g, 66.33 mmol) was suspended
25 in tetrahydrofuran (800 mL) and a solution of *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (20 g, 99.5 mmol) in tetrahydrofuran (300 mL) and triphenylphosphine (34.8 g, 132.66 mmol) were added. The reaction mixture was cooled to 0 °C and diethyl azodicarboxylate (23.1 g, 132.66 mmol) was added dropwise. After 2 hours at room temperature, the reaction was concentrated under
30 reduced pressure to yield crude *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate as an orange oil (69.44 g). HPLC-RT: 14.29 min., 19%, (flow rate: 1 mL/min λ = 254 nm Gradient: 5% to 85%

acetonitrile/0.1M aqueous ammonium acetate gradient over 20 min.; Deltapak C18, 300Å, 5µm, 150 x 3.9 mm column).

c). 3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride salt.

5 The crude *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (69.4 g, 156.30 mmol) was dissolved in acetone (900 mL) and 6N aqueous hydrochloric acid (300 mL) was slowly added dropwise. The reaction was then heated at 45 °C which yielded a precipitate. After 1.5 hours, the precipitate was collected by vacuum filtration, washed with minimal acetone and
10 dried on the lyophilizer to yield 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride salt as a yellow solid (16.61 g, 39.8 mmol). HPLC-RT: 6.16 min. (flow rate: 1 mL/min λ= 254 nm Gradient: 5% to 85% acetonitrile/0.1M aqueous ammonium acetate gradient over 20 min.; Deltapak C18, 300A, 5µm, 150 x 3.9 mm column); m/z (*MH*⁺)= 345.0.

15 d). 1-[4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-(dimethylamino)-1-ethanone.

3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride salt (3g, 7.19 mmol) was suspended in dichloromethane (350 mL) then N,N-dimethyl glycine (1.02 g, 9.88 mmol), 1-hydroxy-7-azabenzotriazole (1.08 g, 7.91 mmol), 1-
20 (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.89 g, 9.89 mmol), and N-ethyl-N-isopropylamine (5.06 g, 39.2 mmol) were added over 4 days. The reaction was diluted with dichloromethane (300 mL) then washed with water (150 mL) and brine (150 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 1-[4-(4-amino-3-iodo-1*H*-
25 pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-(dimethylamino)-1-ethanone as a tan solid (2.74 g, 6.39 mmol). HPLC-RT: 7.40 min. (flow rate: 1 mL/min λ= 254 nm Gradient: 5% to 85% acetonitrile/0.1M aqueous ammonium acetate gradient over 20 min.; Deltapak C18, 300Å, 5µm, 150 x 3.9 mm column); m/z (*MH*⁺)= 430.3.

e). 1-(4-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)-3-fluorophenyl]-1*H*-
30 pyrazolo[3,4-*d*]pyrimidin-1-yl}piperidino)-2-(dimethylamino)-1-ethanone.

1-[4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-(dimethylamino)-1-ethanone (100 mg, 0.233 mmol) was dissolved in ethylene glycol

dimethylether (10 mL) and water (1.5 mL). *N*-(1,3-benzoxazol-2-yl)-*N*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (103 mg, 0.291 mmol), palladium tetrakis(triphenylphosphine) (13 mg, 0.051 mmol) and sodium carbonate (62 mg, 0.583 mmol) were added and the reaction was heated at 80 °C for 24 hours.

- 5 The reaction was concentrated under reduced pressure. The remaining residue was partitioned between dichloromethane (100 mL) and minimal water. The organic layer was concentrated under reduced pressure and triturated with diethylether (25 mL) to yield a yellow-brown solid (172 mg). Purification by RP-HPLC (Waters PrepLC 4000, flow rate: 10 mL/min. λ = 254 nm Gradient: 15% to 35% acetonitrile/0.1M aqueous ammonium acetate gradient over 40 minutes; Deltapak C18, 300Å, 15 μ m, 40 x 100 mm column) afforded 1-(4-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}piperidino)-2-(dimethylamino)-1-ethanone as an off-white solid (64 mg, 0.121 mmol). HPLC-RT: 7.27 min. (flow rate: 1 mL/min λ = 254 nm Gradient: 5% to 95% acetonitrile/0.1M aqueous ammonium acetate gradient over 20 min.; Waters Symmetry Shield C18, 3.5 μ m, 50 x 2.1 mm column); m/z (MH^+) = 530.2.

Example 337 1-(4-{4-amino-3-[4-(1,3-benzothiazol-2-ylamino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}piperidino)-2-(dimethylamino)-1-ethanone

HPLC-RT: 10.09 min. (flow rate: 1 mL/min λ = 254 nm Gradient: 5% to 85% acetonitrile/0.1M aqueous ammonium acetate gradient over 20 min.; Deltapak C18, 300Å, 5 μ m, 150 x 3.9 mm column); m/z (MH^+) = 546.2.

Examples 338 – 364

- 25 a) Representative procedure for alkylation: Sodium hydride (60%, 0.138 g, 3.45 mmol) was added to a suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.750 g, 2.87 mmol) in DMF (9 mL), and the mixture was stirred at ambient temperature for 1 hour until a homogeneous solution was obtained. The alkyl bromide (4.03 mmol) was added, and the mixture was stirred at ambient temperature under an atmosphere of nitrogen for 14 h. The solvent was removed under reduced pressure and the resulting solid was triturated sequentially with water (25 mL) and then ether/petroleum ether (4:1, 50 mL) to yield the product.

- b) Representative procedure for Suzuki coupling: A suspension of the aryl iodide (2.28 mmol), *tert*-butyl *N*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.08 g, 3.19 mmol), tetrakis(triphenylphosphine) palladium (0.105 g, 0.091 mmol), sodium bicarbonate (0.478 g, 5.69 mmol) in *N,N*-dimethylformamide (12 mL) and water (2 mL) was heated at 90 °C for 14 hours under an atmosphere of nitrogen. The solvent was removed under reduced pressure, and the residue was partitioned between saturated aqueous sodium chloride (50 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted further with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using ethyl acetate/heptane (9:1) as a mobile phase afforded the protected aniline product.
- c) Representative procedure for deprotection: To a 50 mL flask containing a solution of hydrogen chloride in dioxane (4 M, 6 mL) and ethanol (6 mL) was added the protected aniline (1.05 mmol). An air condenser was affixed to the flask, and the mixture was stirred at 50 °C under an atmosphere of nitrogen. After 16 hours, the reaction mixture was cooled to ambient temperature, and the solvent was removed under reduced pressure. The residue was partitioned between aqueous hydrochloric acid (0.5 M, 30 mL) and ether (20 mL). The organic layer was separated and discarded. The aqueous layer was basified with saturated aqueous sodium bicarbonate (30 mL), and the resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate extracts were dried over magnesium sulfate, filtered, and concentrated to afford the aniline product.
- d) Representative procedure for sulfonylation: The aniline (1.0 mmol) was added to a solution of 2,3-dichlorobenzenesulfonyl chloride (0.263 g, 1.07 mmol) and 4-dimethylaminopyridine (0.005 g, 0.041 mmol) in pyridine (5 mL), and the resulting solution was stirred under an atmosphere of nitrogen for 3 days. Methanol/dichloromethane (1:19, 100 mL) was added and the resulting mixture was extracted with half-saturated aqueous sodium bicarbonate (3 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to

afford the sulfonamide product.

- e) Representative procedure for transesterification: The ethyl ester (2.76 mmol) was added to a solution of triethylamine (3.8 mL, 28 mmol) and methanol (30 mL). A reflux condenser was affixed to the reaction vessel, and the reaction mixture was heated at 75 °C under an atmosphere of nitrogen. After 24 h, the reaction was allowed to cool to ambient temperature, and the solvent was removed under reduced pressure to afford the methyl ester product.
- f) Alternate procedure for transesterification: A solution of the ethyl ester (0.279 mmol) and sodium methoxide (0.015 g, 0.279 mmol) in methanol (2 mL) was heated in a sealed tube at 75 °C for 2 h. The reaction was cooled to ambient temperature. Methanol/dichloromethane (1:19, 100 mL) was added and the resulting mixture was extracted with half-saturated aqueous sodium bicarbonate (3 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford the methyl ester product.
- g) Representative procedure for amide formation: In a resealable Schlenk flask, the ester (0.056 mmol) was suspended in an amine solvent (1 mL). The flask was sealed with a teflon screwcap and heated at 80 °C for 2 days. The reaction was cooled to ambient temperature to afford the amide product.
- h) Representative procedure for primary amide formation: A sealable Schlenk flask was charged with the methyl ester (0.086 mmol). A solution of methanol saturated with ammonia (1 mL) was added, and the Schlenk flask was sealed and heated at 90 °C for 24 h. The reaction was cooled to ambient temperature, and the solvent was removed under reduced pressure to afford the primary amide product.
- i) Representative procedure for urea formation: The aniline (0.152 mmol) was dissolved in pyridine (1 mL) and the solution was cooled to -20 °C. *m*-Tolyl isocyanate (0.143 mmol) was added, and the solution was allowed to warm naturally to ambient temperature. After 6 h, the product was concentrated under reduced pressure to afford the urea product.

30

Example 338 Ethyl 2-[4-amino-3-(4-[[2,3-dichlorophenyl)sulfonyl]amino]-3-

fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate

The representative procedures for alkylation (using ethyl bromoacetate as the alkyl bromide), Suzuki coupling, deprotection, and sulfonylation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 12.4-13.9 min) afforded ethyl 2-[4-amino-3-(4-
5 {[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate as a white solid (0.011 g, 0.020 mmol): RP-HP (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a
10 Hypersil HS C18, 250 x 4.6 mm column) *R*_t 9.78 min. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.84 (s, 1H), 8.25 (s, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.54 (t, 1H), 7.43 (m, 3H), 5.21 (s, 2H), 4.15 (qt, 2H), 1.20 (t, 3H); MS: MH⁺ 539.

Example 339 *N*1-{4-[4-Amino-1-(2-morpholino-2-oxoethyl)-1*H*-pyrazolo[3,4-
15 *d*]pyrimidin-3-yl]-2-fluorophenyl}-2,3-dichloro-1-benzenesulfonamide

Ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate was treated with morpholine using the representative procedure for amide formation. Purification by
20 preparative HPLC (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 9.3-9.8 min) afforded *N*1-{4-[4-amino-1-(2-morpholino-2-oxoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl}-2,3-dichloro-1-benzenesulfonamide as a white solid (0.005 g, 0.009 mmol): RP-HP (25 to 100 % acetonitrile in 0.1 M aqueous
25 ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) *R*_t 8.22 min. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.82 (s, 1H), 8.21 (s, 1H), 7.96 (d, 1H), 7.94 (m, 1H), 7.53 (t, 1H), 7.39 (m, 3H), 6.97 (br, 2H), 5.32 (s, 2H), 3.5 (m, 8H); MS: MH⁺ 580.

Example 340 *N*1-(4-{4-Amino-1-[2-(4-methylpiperazino)-2-oxoethyl]-1*H*-
30 pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide

Ethyl 2-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate was treated with 1-methylpiperazine using the representative procedure for amide formation. Purification by preparative HPLC (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 6.4-7.0 min) afforded *N*1-(4-{4-amino-1-[2-(4-methylpiperazino)-2-oxoethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide as a white solid (0.005 g, 0.009 mmol): RP-HP (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) R_t 6.83 min. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.20 (s, 1H), 7.96 (d, 1H), 7.88 (d, 1H), 7.50 (t, 1H), 7.36 (m, 3H), 5.31 (s, 2H), 3.45 (m, 4H), 2.50 (m, 4H), 2.30 (s, 3H), MS: MH⁺ 593.

Example 341 *N*1-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-*N*1-methyl-2-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide

A solution of (+)-pseudoephedrine (0.037 g, 0.224 mmol) in ethylene glycol dimethyl ether (0.75 mL) was treated with a solution of *n*-butyllithium (2.5 M in hexanes, 0.060 mL, 0.150 mmol). After 20 min, this solution was transferred via cannula into a solution of ethyl 2-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.040 g, 0.074 mmol) in *N,N*-dimethylformamide (0.75 mL). The resulting solution was stirred at 50 °C for 15 h. It was then cooled to ambient temperature and partitioned between methanol/dichloromethane (1:9, 50 mL), and water (15 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 11.88-12.65 min) afforded *N*1-[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*1-methyl-2-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide as an off-white solid (0.010 g, 0.015 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1

mL/min using a Hypersil HS C18, 250 x 4.6 mm column) R_t 9.63 min; MS: (MH)⁺ 658.

5 Example 342 *N*1-[(1*S*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-*N*1-methyl-2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide

Using a procedure similar to that above, (+)-ephedrine hydrochloride (0.061 g, 0.302 mmol) and ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.054 g, 0.10 mmol) were
10 combined. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 11.4-11.9 min) afforded *N*1-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*1-methyl-2-[4-amino-3-(4-{[(2,3-
15 dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide
as an off-white solid (0.010 g, 0.015 mmol): RP-HPLC (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) R_t 9.36 min; MS: (M-H)⁻ 656.

20 Example 343 *N*1-[4-(4-Amino-1-{2-[(2*S*)-2-(hydroxymethyl)tetrahydro-1*H*-1-pyrrolyl]-2-oxoethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl]-2,3-dichloro-1-benzenesulfonamide

Using a procedure similar to that above, (*R*)-pyrrolidinemethanol (0.038 mL, 0.385 mmol) and ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.060 g, 0.111 mmol) were
25 combined. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.45-9.90 min) afforded *N*1-[4-(4-amino-1-{2-[(2*S*)-2-(hydroxymethyl)tetrahydro-1*H*-1-pyrrolyl]-2-oxoethyl}-1*H*-pyrazolo[3,4-
30 *d*]pyrimidin-3-yl)-2-fluorophenyl]-2,3-dichloro-1-benzenesulfonamide as an off-white solid (0.024 g, 0.040 mmol): RP-HPLC (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250

x 4.6 mm column) R_t 8.05 min; MS: (M-H)⁻ 592.

Example 344 *N*1-[4-(4-Amino-1-{2-[(2*R*)-2-(hydroxymethyl)tetrahydro-1*H*-1-pyrrolyl]-2-oxoethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl]-2,3-dichloro-1-benzenesulfonamide

Using a procedure similar to that above, (*S*)-pyrrolidinemethanol (0.038 mL, 0.385 mmol) and ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.060 g, 0.111 mmol) were combined. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.15-9.70 min) afforded *N*1-[4-(4-amino-1-{2-[(2*R*)-2-(hydroxymethyl)tetrahydro-1*H*-1-pyrrolyl]-2-oxoethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl]-2,3-dichloro-1-benzenesulfonamide as an off-white solid (0.022 g, 0.037 mmol): RP-HPLC (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) R_t 7.98 min; MS: (M-H)⁻ 592.

Example 345 Methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate

Using the representative procedure for transesterification, ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (1.49 g, 2.76 mmol) was converted to the corresponding methyl ester. A portion of the crude material was purified by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 11.0-12.3 min) to afford methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate as a white solid (0.016 g, 0.030 mmol): RP-HP (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) R_t 9.22 min. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.84 (s, 1H), 8.25 (s, 1H), 7.96 (m, 2H), 7.60 (m, 1H), 7.56 (m, 3H), 5.23 (s, 2H), 3.68 (s, 3H); MS: MH⁺ 525.

Example 346 2-[4-Amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetic acid

In a resealable Schlenk flask, methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.030 g, 0.057 mmol) was dissolved in methanol / water (1:1, 1 mL). The flask was sealed with a teflon screwcap and heated at 90 °C. After 2 days, the reaction was cooled to ambient temperature. Purification by preparative HPLC (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 6.3-6.7 min) afforded 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetic acid as a white solid (0.006 g, 0.030 mmol): RP-HP (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) R_t 6.42 min. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.13 (s, 1H), 7.97 (d, 1H), 7.62 (d, 1H), 7.36 (t, 1H), 7.19 (m, 3H), 7.15 (d, 1H), 4.59 (s, 2H); MS: (M-H)⁻ 509.

Example 347 *N*1-[2-(Dimethylamino)ethyl]-2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide

The representative procedure for amide formation was used in the reaction of methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.035 g, 0.067 mmol) with *N,N*-dimethylethylenediamine (1 mL). Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 6.85-7.45 min) afforded *N*1-[2-(dimethylamino)ethyl]-2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide as an off-white solid (0.008 g, 0.014 mmol): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.20 (br, 1H), 8.22 (m, 2H), 7.96 (d, 1H), 7.80 (d, 1H), 7.45 (t, 1H), 7.31 (m, 3H), 6.90 (br, 2H), 4.96 (s, 2H), 3.40 (m, 2H), 2.75 (m, 2H), 2.07 (s, 6H); MS: (M-H)⁻ 579.

Example 348 *N*1-[2-(Diethylamino)ethyl]-2-[4-amino-3-(4-{{(2,3-dichlorophenyl)sulfonyl}amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide

5 The representative procedure for amide formation was used in the reaction of methyl 2-[4-amino-3-(4-{{(2,3-dichlorophenyl)sulfonyl}amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.035 g, 0.067 mmol) with *N,N*-diethylethylenediamine (1 mL). Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an
10 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 7.12-7.98 min) afforded *N*1-[2-(diethylamino)ethyl]-2-[4-amino-3-(4-{{(2,3-dichlorophenyl)sulfonyl}amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide as an off-white solid (0.017 g, 0.028 mmol): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.22 (s, 1H), 8.12 (br, 1H), 7.96 (d, 1H), 7.78 (d, 1H), 7.44 (t, 1H), 7.31 (m, 3H); 6.95 (br, 2H), 4.96 (s,
15 2H), 3.35 (m, 2H), 2.82 (m, 2H), 2.50 (m, 4H), 1.05 (t, 6H); MS: (M-H)⁻ 607.

Example 349 2-(Dimethylamino)ethyl 2-[4-amino-3-(4-{{(2,3-dichlorophenyl)sulfonyl}amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate

20 The representative procedure for amide formation was used in the reaction of methyl 2-[4-amino-3-(4-{{(2,3-dichlorophenyl)sulfonyl}amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.035 g, 0.067 mmol) with *N,N*-dimethylethanolamine (1 mL). Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an
25 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 7.50-8.07 min) afforded 2-(dimethylamino)ethyl 2-[4-amino-3-(4-{{(2,3-dichlorophenyl)sulfonyl}amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate as an off-white solid (0.008 g, 0.014 mmol): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.24 (s, 1H), 7.96 (d, 1H), 7.83 (d, 1H), 7.48 (t, 1H), 7.32 (m, 3H), 5.23 (s, 2H), 4.29 (t, 2H), 2.86 (m, 2H), 2.39 (s,
30 6H); MS: (M-H)⁻ 580.

Example 350 *N*1-[3-(Dimethylamino)propyl]-2-[4-amino-3-(4-{{(2,3-

dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide

The representative procedure for amide formation was used in the reaction of methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.025 g, 0.048 mmol) with 3-(dimethylamino)propylamine (1 mL). Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 6.7-7.3 min) afforded *N*1-[3-(dimethylamino)propyl]-2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide as an off-white powder (0.015 g, 0.025 mmol): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.20 (m, 1H), 7.96 (m, 1H), 7.76 (m, 1H), 7.43 (t, 1H), 7.30 (m, 2H), 4.93 (s, 2H), 3.12 (m, 2H), 2.82 (m, 2H), 2.50 (s, 6H), 1.73 (m, 2H); MS (M-H)⁻ 593.

Example 351 2-[4-Amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide

The representative procedure for primary amide formation was used to convert methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate (0.045 g, 0.086 mmol) to the corresponding primary amide. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 6.9-8.5 min) afforded 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetamide as an off-white powder (0.015 g, 0.029 mmol): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.83 (br, 2H), 8.84 (br, 1H), 7.93 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 7.62 (s, 1H), 7.50 (m, 2H), 7.36 (m, 1H); 3.87 (s, 2H); MS (M-H)⁻ 508.

Example 352 Ethyl 2-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)acetate

The representative procedures for alkylation (using ethyl bromoacetate as the alkyl bromide), Suzuki coupling, deprotection, and urea formation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M

aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 12.1-13.5 min) afforded ethyl 2-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)acetate as a yellow powder (0.015 g, 0.032 mmol): ^1H NMR (DMSO-*d*₆, 400 MHz) δ 9.07 (br, 1H), 8.73 (br, 1H), 8.38 (t, 1H), 8.26 (s, 1H), 7.48 (m, 2H), 7.32 (s, 1H), 7.25 (d, 1H), 7.19 (t, 1H), 6.82 (d, 1H), 5.23 (s, 2H), 4.17 (qt, 2H), 2.30 (s, 3H), 1.21 (t, 3H); MS: (M-H)⁻ 462.

Example 353 *N*-{4-[4-Amino-1-(2-morpholino-2-oxoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl}-*N*'-(3-methylphenyl)urea
Ethyl 2-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)acetate (0.025 g, 0.054 mmol) was converted to the corresponding methyl ester using the representative procedure for transesterification. This product was dissolved in morpholine (1 mL) and the solution was heated at 50 °C in a sealed tube for 2 days. The reaction was cooled to ambient temperature, concentrated, and purified by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 9.3-10.2 min) to afford *N*-{4-[4-amino-1-(2-morpholino-2-oxoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl}-*N*'-(3-methylphenyl)urea as a yellow solid (0.009 g, 0.018 mmol): ^1H NMR (DMSO-*d*₆, 400 MHz) δ 9.07 (s, 1H), 8.72 (s, 1H), 8.37 (t, 1H), 8.23 (s, 1H), 7.45 (m, 2H), 7.33 (t, 1H), 7.27 (m, 1H), 7.19 (t, 1H), 6.83 (d, 1H), 5.34 (s, 2H), 3.5 (m, 8H), 2.30 (s, 3H); MS (M-H)⁻ 503.

Example 354 *N*-(4-{4-amino-1-[2-(4-methylpiperazino)-2-oxoethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-*N*'-(3-methylphenyl)urea

A procedure similar to that above, except using 1-methylpiperazine (1 mL) instead of morpholine as solvent, followed by purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 7.1-7.8 min) afforded *N*-(4-{4-amino-1-[2-(4-methylpiperazino)-2-oxoethyl]-1*H*-pyrazolo[3,4-

d]pyrimidin-3-yl}-2-fluorophenyl)-*N*'-(3-methylphenyl)urea as an off-white solid (0.008 g, 0.015 mmol): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.07 (s, 1H), 8.72 (s, 1H), 8.37 (t, 1H), 8.22 (s, 1H), 7.45 (m, 2H), 7.32 (s, 1H), 7.25 (m, 1H), 7.19 (t, 1H), 6.90 (br, 2H), 6.83 (d, 1H), 5.33 (s, 2H), 3.39 (m, 4H), 2.40 (m, 4H), 2.30 s, 3H; MS (M-H)⁻ 516.

Example 355 Ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanoate

The representative procedures for alkylation (using ethyl 2-bromopropionate as the alkyl bromide), Suzuki coupling, deprotection, and sulfonylation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 10.1-11.0 min) afforded ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanoate (0.016 g, 0.029 mmol) as a gray solid: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.84 (br, 1H), 8.24 (s, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.54 (t, 1H); 7.41 (m, 3H), 7.0 (br, 1H), 5.61 (qt, 1H), 4.10 (qt, 2H), 1.73 (d, 3H), 1.11 (t, 3H); MS (M-H)⁻ 551.

Example 356 Methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanoate (4032811)

The representative procedure for transesterification was used to convert ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanoate (0.400 g, 0.723 mmol) to the corresponding methyl ester. Purification of a portion of the material by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 12.4-12.9 min) afforded methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanoate (0.008 g, 0.015 mmol) as a gray solid: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.84 (s, 1H), 8.24 (s, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.54 (t, 1H), 7.40 (m, 3H), 4.10 (m, 1H), 3.62 (s, 3H), 1.73 (d,

3H); MS (MH)⁺ 539.

Example 357 2-[4-Amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanamide

5 The representative procedure for primary amide formation was used to convert methyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanoate (0.040 g, 0.074 mmol) to the corresponding primary amide. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using
10 an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.1-9.6 min) afforded 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanamide (0.015 g, 0.029 mmol) as a white powder: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.82 (s, 1H), 8.22 (s, 1H), 7.98 (s, 1H), 7.96 (s, 1H), 7.56 (t, 1H), 7.42 (m, 3H), 7.31 (br, 1H), 7.21 (br, 1H), 5.34 (qt, 1H), 1.71 (d, 3H); MS
15 (MH)⁺ 524.

Example 358 Ethyl 2-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanoate

20 The representative procedures for alkylation (using ethyl 2-bromopropionate as the alkyl bromide), Suzuki coupling, deprotection, and urea formation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 13.3-14.3 min) afforded ethyl 2-(4-
25 amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanoate as a white solid (0.022 g, 0.046 mmol): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.06 (s, 1H), 8.73 (s, 1H), 8.37 (t, 1H), 8.25 (s, 1H), 7.46 (m, 2H), 7.32 (s, 1H), 7.25 (m, 1H), 7.19 (t, 1H), 6.83 (d, 1H), 5.63 (qt, 1H), 4.12 (qt, 2H), 2.30 (s, 3H), 1.76 (d, 3H), 1.15 (t, 3H); MS (M-H)⁻ 476.

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Example 359 2-(4-Amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanamide

The representative procedures for alkylation (using ethyl 2-bromopropionate as the alkyl bromide), Suzuki coupling, deprotection, the alternate procedure for transesterification, and the representative procedures for primary amide formation and urea formation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 9.1-10.1 min) afforded 2-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl})-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanamide as a gray solid (0.010 g, 0.022 mmol): ^1H NMR (DMSO-*d*₆, 400 MHz) δ 9.08 (s, 1H), 8.38 (s, 1H), 8.37 (t, 1H), 8.23 (s, 1H), 7.46 (m, 2H), 7.33 (m, 2H), 7.24 (m, 2H), 7.12 (d, 1H), 6.97 (br, 2H), 6.82 (d, 1H), 5.35 (qt, 1H), 2.30 (s, 3H), 1.75 (d, 3H); MS (MH)⁺ 449.

Example 360 Ethyl 4-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanoate

The representative procedures for alkylation (using ethyl 4-bromobutyrate as the alkyl bromide), Suzuki coupling, deprotection, and sulfonylation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 12.8-13.8 min) afforded ethyl 4-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanoate (0.010 g, 0.018 mmol) as an off-white solid: ^1H NMR (DMSO-*d*₆, 400 MHz) δ 10.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.54 (t, 1H), 7.40 (m, 3H), 6.95 (m, 2H), 4.35 (t, 2H), 3.97 (qt, 2H), 2.30 (t, 2H), 2.08 (m, 2H), 1.12 (t, 3H); MS (M-H)⁻ 565.

Example 361 Methyl 4-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanoate

The representative procedures for alkylation (using ethyl 4-bromobutyrate as the alkyl bromide), Suzuki coupling, deprotection, the alternate procedure for transesterification, and the representative procedure for sulfonylation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ

Hypersil HS C18, 250 x 21 mm column, R_t 11.7-12.2 min) afforded methyl 4-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanoate as a yellow solid (0.015 g, 0.027 mmol): ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.84 (br, 1H), 8.23 (s, 1H), 7.95 (m, 2H), 7.52 (m, 1H), 7.40 (m, 3H), 4.35 (t, 2H), 3.52 (s, 3H), 2.32 (t, 2H), 2.09 (m, 2H); MS (MH)⁺ 553.

Example 362 4-[4-Amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanamide

10 The representative procedure for primary amide formation was used to convert methyl 4-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanoate (0.026 g, 0.047 mmol) to the corresponding primary amide. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.0-9.0 min) afforded 4-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanamide as a white solid (0.007 g, 0.013 mmol): ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.82 (s, 1H), 8.24 (s, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.54 (t, 1H), 7.45 (m, 3H), 7.24 (br, 1H), 6.93 (br, 2H), 6.73 (br, 1H), 4.31 (t, 2H), 2.05 (m, 4H); MS (M-H)⁻ 536.

Example 363 Ethyl 4-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)butanoate (4032812)

25 The representative procedures for alkylation (using ethyl 4-bromobutyrate as the alkyl bromide), Suzuki coupling, deprotection, and urea formation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 12.6-13.6 min) afforded ethyl 4-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)butanoate as an off-white powder (0.015 g, 0.030 mmol): ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.06 (s, 1H), 8.72 (s, 1H), 8.36 (t, 1H), 8.24 (s, 1H), 7.47

(m, 2H), 7.32 (s, 1H), 7.22 (m, 1H), 7.19 (t, 1H), 6.82 (d, 1H), 4.37 (t, 3H), 3.99 (qt, 3H), 2.34 (t, 2H), 2.30 (s, 3H), 2.11 (m, 2H), 1.13 (t, 3H); RP-HPLC (25 to 100 % CH₃CN in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) R_t 10.00 min.

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Example 364 4-(4-Amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)butanamide

The representative procedures for alkylation (using ethyl 4-bromobutyrate as the alkyl bromide), Suzuki coupling, deprotection, the alternate procedure for transesterification, and the representative procedures for primary amide formation and urea formation were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.4-9.1 min) afforded 4-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)butanamide as a white solid (0.010 g, 0.022 mmol):
15 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.08 (s, 1H), 8.73 (s, 1H), 8.38 (t, 1H), 8.25 (s, 1H), 7.47 (m, 2H), 7.32 (s, 1H), 7.25 (m, 2H), 7.19 (m, 1H), 6.83 (d, 1H), 6.75 (s, 1H), 4.34 (t, 2H), 2.30 (s, 3H), 2.05 (m, 4H); MS (MH)⁺ 463.

20 Example 365 2-{4-Amino-3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl}-5-(4-methylpiperazino)benzonitrile

A suspension of 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.172 g, 0.66 mmol), sodium hydride (60%, 0.030 g, 0.75 mmol), 2,5-difluorobenzonitrile (0.105 g, 0.75 mmol), and *N,N*-dimethylformamide (2.5 mL) was heated for 24 h at 100 °C.

25 The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was partitioned between dichloromethane (50 mL) and water (10 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

A portion of the material (0.045 g, 0.118 mmol) and cesium carbonate (0.115 g, 0.353 mmol) were suspended in 1-methylpiperazine (1 mL), and the mixture was
30 heated at 110 °C in a sealed tube for 20 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was

acidified with aqueous hydrochloric acid (1 M, 10 mL), and the aqueous phase was extracted with ether (10 mL). The organic phase was discarded, and the aqueous phase was basified with aqueous sodium carbonate (3 M, 10 mL). The aqueous phase was extracted with dichloromethane (3 x 15 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

This material was subjected to a Suzuki coupling using the representative procedure, except that *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine was used in lieu of *tert*-butyl *N*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 7.0-8.6 min) afforded 2-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}-5-(4-methylpiperazino)benzonitrile as a gray solid (0.009 g, 0.017 mmol): ^1H NMR (DMSO-*d*₆, 400 MHz) δ 10.93 (s, 1H), 8.29 (s, 1H), 7.98 (d, 2H), 7.78 (d, 2H), 7.73 (d, 1H), 7.52 (m, 3H), 7.44 (m, 1H), 7.26 (t, 1H), 7.17 (t, 1H), 3.24 (m, 4H), 2.45 (m, 4H), 2.28 (s, 3H); MS (MH)⁺ 543.

Example 366 Ethyl 2-{4-amino-3-[4-(1,3-benzothiazol-2-ylamino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}propanoate

The representative procedure for alkylation (using ethyl 2-bromopropionate as the alkyl bromide) and the representative procedure for Suzuki coupling (except using *N*-(1,3-benzothiazol-2-yl)-*N*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine in lieu of *tert*-butyl *N*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate) were conducted in sequence. Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 14.4-14.9 min) afforded ethyl 2-{4-amino-3-[4-(1,3-benzothiazol-2-ylamino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}propanoate as an off-white solid (0.022 g, 0.046 mmol): ^1H NMR (DMSO-*d*₆, 400 MHz) δ 10.52 (s, 1H), 8.82 (t, 1H), 8.26 (s, 1H), 7.85 (d, 1H), 7.66 (d, 1H), 7.55 (m, 2H), 7.36 (t, 1H), 7.22 (t, 1H), 5.65 (qt, 1H), 4.14 (qt, 2H), 1.77 (d, 3H), 1.14 (t,

3H); MS (MH)⁺ 478.

Example 367 *Cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine*

N2-(4-bromo-2-fluorophenyl)-1,3-benzoxazol-2-amine

To a solution of 4-bromo-2-fluoroaniline (1.00 g, 5.26 mmol) in toluene (25 mL) was added 2-chlorobenzoxazole (0.66 mL, 5.79 mmol). The purple solution was heated at reflux for 30 min and then at 100 °C for 17 h. The resulting white

suspension/purple solution was cooled to room temperature and the precipitate was filtered. The filter cake was washed with five 2-mL portions of heptane to afford *N2-(4-bromo-2-fluorophenyl)-1,3-benzoxazol-2-amine* (1.480 g, 92%) as a light purple powder. RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=12.87 min, 97%; *m/z* 307 (MH⁺).

N2-(4-bromo-2-fluorophenyl)-1,3-benzothiazol-2-amine

To a solution of 4-bromo-2-fluoroaniline (1.00 g, 5.26 mmol) in toluene (25 mL) was added 2-chlorobenzothiazole (0.75 mL, 5.79 mmol). The purple solution was heated at 110-150 °C in a resealable tube for 66 h and then cooled to room

temperature. The resulting brown solution was concentrated to give a purple solid which was triturated with heptane to afford *N2-(4-bromo-2-fluorophenyl)-1,3-benzothiazol-2-amine* (1.699 g, 99%) as a light purple powder. RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=13.82 min, 95%; *m/z* 325 (MH⁺).

N2-(4-bromophenyl)-1,3-benzothiazol-2-amine

N2-(4-bromophenyl)-1,3-benzothiazol-2-amine was prepared from 4-bromoaniline (1.00 g, 5.81 mmol) in a manner similar to that used for *N2-(4-bromo-2-fluorophenyl)-1,3-benzoxazol-2-amine*. The compound was formed as a light purple powder (0.867 g, 49%). RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=13.32 min, 100%; *m/z* 307 (MH⁺).

N2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-

benzoxazol-2-amine

To a solution of *N*2-(4-bromo-2-fluorophenyl)-1,3-benzoxazol-2-amine (1.480 g, 4.819 mmol) in dimethylformamide (15 mL) under nitrogen was added bis(pinacolato)diboron (1.468 g, 5.781 mmol), potassium acetate (1.419 g, 14.45 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complexed with dichloromethane (1:1) (0.119 g, 0.146 mmol). The violet solution was stirred at 80 °C for 18 h and then cooled to room temperature. The resulting dark brown mixture was concentrated *in vacuo* to give a dark brown solid. This material was triturated with dichloromethane, filtered, and the filtrate was concentrated to give a dark brown oil. Purification via flash chromatography on silica gel (eluting with 30% ethyl acetate/heptane) afforded 2.28 g of a yellow solid. This material was triturated with heptane and the solid was collected to afford *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine (0.961 g, 56%) as a white powder. RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) *tr*=13.80 min, 88%; *m/z* 355 (*MH*⁺).

*N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzothiazol-2-amine

*N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzothiazol-2-amine was prepared from *N*2-(4-bromo-2-fluorophenyl)-1,3-benzothiazol-2-amine (1.699 g, 5.258 mmol) in a manner similar to that used for *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as an off-white powder (0.825 g, 42%). RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) *tr*=14.48 min, 90%; *m/z* 371 (*MH*⁺).

*N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzothiazol-2-amine

*N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzothiazol-2-amine was prepared from *N*2-(4-bromophenyl)-1,3-benzothiazol-2-amine (0.909 g, 2.98 mmol) in a manner similar to that used for *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as an off-white powder (0.321 g, 31%). RP-HPLC (25 to 100 % CH₃CN in

0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) $t_r=13.82$ min., 92%; m/z 351 (MH^+).

5 Example 367 *Cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine*

To a solution of *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.150 g, 0.340 mmol) in ethylene glycol dimethyl ether (3 mL) and water (1.5 mL) under nitrogen was added *N2*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine (0.151 g, 0.425 mmol), tetrakis(triphenylphosphine) palladium (0) (0.020 mg, 0.017 mmol), and sodium carbonate monohydrate (0.105 mg, 0.850 mmol). The solution was stirred at 83 °C for 19 h. The resulting yellow mixture was concentrated *in vacuo* to give a yellow oil. Purification by preparative RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 20 min at 21 mL/min using a 8 μm Hypersil HS C18, 250 x 21 mm column, $t_r=5.7$ -8.1 min.) afforded *cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)-cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine* as an off-white solid (0.046 g, 25 %): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.65 (s, 1 H), 8.49 (m, 1 H), 8.25 (s, 1 H), 7.53 (d, 2 H), 7.48 (d, 2 H), 7.26 (t, 1 H), 7.20 (t, 1 H), 4.80 (m, 1 H), 3.51-2.50 (m, 11 H), 2.33-2.32 (m, 4 H), 2.09-2.06 (m, 2 H), 1.80-1.40 (m, 3 H); RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) $t_r=6.95$ min., 99%; m/z 542 (MH^+).

25 Example 368 *Cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzothiazol-2-amine*

*Cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzothiazol-2-amine* was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.227 mmol) and *N2*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-

2-yl)phenyl]-1,3-benzothiazol-2-amine (0.105 g, 0.283 mmol) in a manner similar to that used for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white powder (0.051 g, 41%): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.51 (s, 1 H), 8.80 (m, 1 H), 8.24 (s, 1 H), 7.85 (d, 1 H), 7.65 (d, 1 H), 7.51 (m, 2 H), 7.36 (t, 1 H), 7.20 (t, 1 H), 4.82 (m, 1 H), 3.51-2.25 (m, 14 H), 2.15-2.10 (m, 2 H), 1.80-1.50 (m, 4 H); RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=7.63 min., 100%; *m/z* 558 (*MH*⁺).

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Example 369 *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-1,3-benzothiazol-2-amine
Cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-1,3-benzothiazol-2-amine was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.227 mmol) and *N2*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzothiazol-2-amine (0.100 g, 0.283 mmol) in a manner similar to that used for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white powder (0.035 g, 28%): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.71 (s, 1 H), 8.23 (s, 1 H), 7.98 (d, 2 H), 7.84 (d, 1 H), 7.65 (d, 3 H), 7.35 (t, 1 H), 7.19 (t, 1 H), 4.80 (m, 1 H), 3.50 (m, 1 H), 2.67- 2.09 (m, 15 H), 1.71-1.57 (m, 4 H); RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=7.47 min., 100%; *m/z* 540 (*MH*⁺).

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Example 370 *Trans-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-1,3-benzoxazol-2-amine
Trans-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-1,3-benzoxazol-2-amine was prepared from *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.036 g, 0.082 mmol) and *N2*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-

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benzoxazol-2-amine (0.034 g, 0.10 mmol) in a manner similar to that used for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white powder (0.021 g, 50%): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.86 (s, 1 H), 8.23 (s, 1 H), 7.93 (d, 2 H), 7.66 (d, 2 H), 7.51 (t, 1 H), 7.25 (t, 1 H), 7.16 (t, 1 H), 4.65 (m, 1 H), 3.51 (m, 1 H), 2.67-1.91 (m, 17 H), 1.49-1.46 (m, 2 H); RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=7.17 min., 100%; *m/z* 524 (*MH*⁺).

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Example 371 *Trans-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine

Trans-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine was prepared from *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.227 mmol) and *N2*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine (0.151 g, 0.425 mmol) in a manner similar to that used for the *cis*-isomer. The compound was formed as a white powder (0.053 g, 43%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.63 (s, 1 H), 8.45 (m, 1 H), 8.24 (s, 1 H), 7.55-7.48 (m, 4 H), 7.25 (t, 1 H), 7.17 (t, 1 H), 4.65 (m, 1 H), 3.36 (m, 1 H), 3.31-1.93 (m, 16 H), 1.46-1.23 (m, 3 H); RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=6.73 min., 99%; *m/z* 542 (*MH*⁺).

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Example 372 *Trans-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzothiazol-2-amine

Trans-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzothiazol-2-amine was prepared from *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.227 mmol) and *N2*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-

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- dioxaborolan-2-yl)phenyl]-1,3-benzothiazol-2-amine (0.105 g, 0.283 mmol) in a manner similar to that used for the *cis*-isomer. The compound was formed as a white powder (0.052 g, 41%): ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.51 (s, 1 H), 8.79 (m, 1 H), 8.24 (s, 1 H), 7.85 (d, 1 H), 7.66 (d, 1 H), 7.51 (m, 2 H), 7.36 (t, 1 H), 7.20 (t, 1 H), 4.66 (m, 1 H), 3.69 (m, 1 H), 2.89-1.94 (m, 17 H), 1.50-1.47 (m, 2 H); RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) t_r =6.30 min., 99%; m/z 558 ($M\text{H}^+$).
- 10 Example 373 *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine
- 1,1'-Thiocarbonyldi-2(1*H*)-pyridone (0.086 g, 0.369 mmol) was added to a solution of *cis*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.150 g, 0.369 mmol) in pyridine (7 mL) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The resulting orange solution was partitioned between dichloromethane (10 mL) and water (10 mL). The organic layer was separated and washed with 0.5 N HCl (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. 2-Amino-*m*-cresol (0.045 g, 0.369 mmol) was added to a suspension of the resulting orange solid and toluene (10 mL), and the mixture was heated at 80 °C for 1 h. 1,3-Dicyclohexylcarbodiimide (0.114 g, 0.554 mmol) was added and the reaction mixture was heated at 80 °C for an additional 18 h. The resulting orange brown solution was cooled to room temperature and concentrated to afford a light brown glassy solid. Purification by preparative HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 20 min at 21 mL/min using a 8 μ Hypersil HS C18, 250 x 21 mm column, t_r =8.1-10.3 min.) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine as an off-white solid (0.024 g, 12 %): ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.81 (s, 1 H), 8.24 (s, 1 H), 7.96 (d, 2 H), 7.66 (d, 2 H), 7.33 (d, 1 H), 7.06 (m, 2 H), 4.80 (m, 1 H), 3.391 (m, 1 H), 2.67-2.10 (m, 18 H), 1.71-1.60 (m, 4 H); RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a

Hypersil HS C18, 250 x 4.6 mm column) $t_r=7.57$ min., 99%; m/z 538 (MH^+).

Example 374 *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-chloro-1,3-benzoxazol-2-amine

- 5 *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-chloro-1,3-benzoxazol-2-amine was prepared from *cis*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.246 mmol) and 2-amino-4-chlorophenol (0.035 g, 0.246 mmol) in a manner similar to that used for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine. The compound was formed as a pale yellow solid (0.020 g, 15%):
- 1H NMR (DMSO- d_6 , 400 MHz) δ 11.03 (s, 1 H), 8.24 (s, 1 H), 7.92 (d, 2 H), 7.67 (d, 2 H), 7.56 (m, 2 H), 7.20 (m, 1 H), 7.16 (t, 1 H), 4.81 (m, 1 H), 3.41-1.60 (m, 20 H);
- 10 RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) $t_r=7.83$ min., 99%; m/z 558 (MH^+).

Example 375 *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-methyl-1,3-benzoxazol-2-amine

- 20 *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-methyl-1,3-benzoxazol-2-amine was prepared from *cis*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.057 g, 0.140 mmol) and 2-amino-*p*-cresol (0.017 g, 0.140 mmol) in a manner similar to that used for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.010 g, 13%): 1H NMR (DMSO- d_6 , 400 MHz) δ 10.81 (s, 1 H), 8.23 (s, 1 H), 7.93 (d, 2 H),
- 25 7.66 (d, 2 H), 7.38 (d, 1 H), 7.30 (s, 1 H), 6.96 (d, 1 H), 4.80 (m, 1 H), 2.60-2.07 (m, 12 H), 2.39 (s, 3 H), 2.15 (s, 3 H), 1.71-1.59 (m, 5 H); RP-HPLC (25 to 100 %
- 30

CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=7.48 min., 90%; *m/z* 538 (*MH*⁺).

Example 376 *Cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine*

*Cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine* was prepared from *cis-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine* (0.100 g, 0.246 mmol) and 6-amino-2,4-xlenol (0.034 g, 0.246 mmol) in a manner similar to that used for *cis-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine*. The compound was formed as an off-white solid (0.031 g, 23%): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.85 (s, 1 H), 8.23 (s, 1 H), 7.93 (d, 2 H), 7.65 (d, 2 H), 7.11 (s, 1 H), 6.80 (s, 1 H), 4.80 (m, 1 H), 2.60-2.17 (m, 12 H), 2.41 (s, 3 H), 2.37 (s, 3 H), 2.22 (s, 3 H), 1.71-1.59 (m, 5 H); RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) tr=8.00 min., 93%; *m/z* 552 (*MH*⁺).

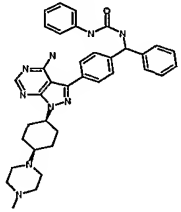
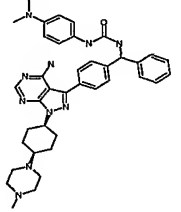
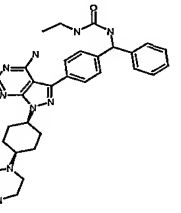
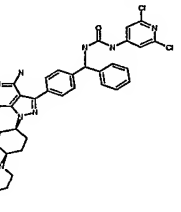
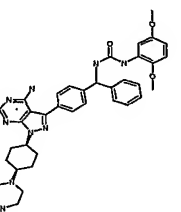
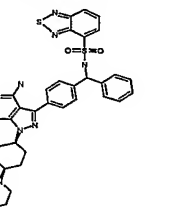
Example 377 *N2-[4-(4-amino-1-{4-[1-(1-methylpiperid-4-yl)piperidyl]})-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl]-5-chloro-2-thiophenesulfonamide*

This compound was prepared from *N1-4-(4-amino-1-{4-[1-(1-methylpiperid-4-yl)piperidyl]})-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenylaniline* (100 mg, 0.236 mmol) using the method described hereinabove, to afford *N2-[4-(4-amino-1-{4-[1-(1-methylpiperid-4-yl)piperidyl]})-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl]-5-chloro-2-thiophenesulfonamide* (51 mg); RP-HPLC conditions : 10 to 90 % CH₃CN in 0.1 N aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 2 mL/min using a Waters Symmetry C18, 300Å, 5 μm, 250 x 4.6 mm column R_t 11.219 min., 98.5 % and *m/z* (*MH*⁺) 605.2.

Examples 378- 383 General synthesis of urea and sulfonamide analogs of *cis-3-{4-[amino(phenyl)methyl]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine*.

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These anaologs were prepared from *cis*-3-{4-[amino(phenyl)methyl]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (50 mg, 0.10 mmol) using the method described hereinabove, to afford the following examples:

	13.815	100	616.3	378
	13.122	100	659.5	379
	11.64	100	568.3	380
	14.99	97.8	685.5	381
	14.43	100	676.6	382
	13.68	100	695	383

Analytical RP-HPLC conditions : 10 to 90 % CH₃CN in 0.1 N aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 2 mL/min using a Waters Symmetry C18, 5 µm, 300Å, 250 x 4.6 mm column.

5 Example 384 *Trans-N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzyl)-*N'*-(3-methylphenyl)

A mixture containing *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (850 mg, 1.93 mmol), *tert*-butyl *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]carbamate (1.25 equiv., 812 mg, 2.41
10 mmol), *tetrakis*-(triphenylphosphine)palladium (135 mg) and sodium carbonate (2.5 equiv., 511 mg, 4.83 mmol) in degassed water (10 mL) and DME (30 mL) was heated and stirred at 85 °C for 16 h. The solvent was removed under reduced pressure to give a brown foam which was purified by column chromatography over silica gel using 10% methanol and 1% ammonium hydroxide in dichloromethane as
15 the eluent. *Trans-tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzyl)carbamate was formed as an off white foam (800 mg, 80%).

A solution of *tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzyl)carbamate (800 mg) in TFA (4 mL) and
20 dichloromethane (4 mL) was stirred at ambient temperature for 2 h. The solvent was removed *in vacuo* and the oily residue was basified with saturated aqueous sodium hydrogen carbonate solution and the aqueous layer washed with dichloromethane (3 x 20 mL). The aqueous layer was concentrated and DMF added (20 mL). The salts were removed by filtration and the DMF was removed *in vacuo*.
25 The residue was purified by column chromatography over silica gel using 10% methanol in dichloromethane as the eluent to afford 3-[4-(aminomethyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a yellow solid (70 mg, 11%).

m-Tolyl isocyanate (1.1 equiv., 13.7 mg, 0.1 mmol) was added to a solution of 3-[4-(aminomethyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (35 mg, 0.083 mmol) in pyridine (0.5 mL) and then stirred for
30 2 days. The reaction mixture was purified using mass actuated preparative RP-HPLC (Micromass/Gilson, Hypersil BDS C18, 5 µm, 100 x 21.2 mm column; 0 –

100% acetonitrile and 0.05M ammonium acetate, buffered to pH 4.5, over 12.5 min at 25 mL/min) to give *trans*-*N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzyl)-*N'*-(3-methylphenyl)urea (17 mg, 37 %); ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.46 (2H, *m*), 2.05 (4H, *m*), 2.18 (2H, *m*), 2.25 (3H, *s*), 2.33 (4H, *m*), 2.45 – 2.53 (8H, *m*), 4.38 (2H, *br d*), 4.65 (1H, *m*), 6.52 (1H, *t*), 6.66 (1H, *d*), 7.10 (1H, *t*), 7.19 (1H, *br d*), 7.26 (1 H, *br s*), 7.46 (2 H, *d*), 7.63 (2H, *d*), 8.23 (1H, *s*) and 8.51 (1H, *s*) and *m/z* (*MH*⁺) 554.2.

Example 385 *Trans*-*N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzyl)-*N'*-(3-methoxyphenyl)urea
10 The same method, and scale, as described in Example 240 was used to prepare *trans*-*N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzyl)-*N'*-(3-methoxyphenyl)urea (17 mg, 36 %); ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.46 (2H, *m*), 2.05 (4H, *m*), 2.18 (2H, *m*), 2.35 (4H, *m*), 2.45 – 2.53 (8H, *m*), 3.70 (3H, *s*), 4.38 (2H, *br d*), 4.65 (1H, *m*), 6.49 (1H, *m*), 6.67 (1H, *m*), 6.90 (1H, *br d*), 7.12 (1H, *t*), 7.17 (1H, *m*), 7.46 (2 H, *d*), 7.63 (2H, *d*), 8.23 (1H, *s*) and 8.62 (1H, *s*) and *m/z* (*MH*⁺) 570.2.

Example 386 *cis*-*N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide
20

2,2-dimethyl-3-phenylpropanenitrile

A solution of *N*-isopropylcyclohexyl amine (2.8 g, 19.72 mmol) in anhydrous tetrahydrofuran (25 mL) at –78°C was treated with 1.6 M *n*-butyl lithium in hexane
25 (12.23 mL, 19.72 mmol) drop-wise over 15 minutes. The reaction solution was stirred for 10 min at –78°C. The solution turned yellow from colorless.
Isobutyronitrile (1.36 g, 19.72 mmol) was added to the reaction solution, and the reaction mixture was stirred for a further 10 min at –78°C. This solution was syringed into a solution of benzyl chloride (2.62 g, 20.71 mmol) in anhydrous
30 tetrahydrofuran at –78°C under a nitrogen atmosphere. The reddish/brown reaction was solution stirred for 1 h at –78°C. The dry ice/ acetone bath was then removed, and the solution stirred at room temperature for 5 h. The reaction solution was

quenched with saturated aqueous ammonium chloride solution (10 mL). Ethyl acetate (25 mL) was added to the quenched reaction solution. The layers were partitioned and the aqueous layer was extracted with ethyl acetate (150 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield 3.18 g of crude material. The crude material was partitioned between 2 N hydrochloric acid solution and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated to give 2.18 g (69%) 2,2-dimethyl-3-phenylpropanenitrile. ¹H NMR (DMSO-d₆, 400 MHz) δ 7.369-7.333 (m, 2H), 7.309-7.270 (m, 3H), 2.832 (s, 2H), 1.294 (s, 6H). This compound was used in subsequent reaction with out further analysis.

2,2-dimethyl-3-phenylpropanoic acid

A solution of 2,2-dimethyl-3-phenylpropanenitrile (1.0 g, 6.28 mmol) in ethylene glycol (5 mL) was treated with solid potassium hydroxide (1.06 g, 18.84 mmol). The reaction mixture was stirred for 48 h at 196°C under a nitrogen atmosphere. Ethylene glycol was removed under vacuum distillation. 1 N Sodium hydroxide solution (25 mL) and ethyl acetate (15 mL) were added to the brown residue. The layers were separated, and the aqueous layer was extracted with ethyl acetate (375 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to give 0.856 g (76%) of 2,2-dimethyl-3-phenylpropanoic acid. ¹H NMR (DMSO-d₆, 400 MHz) δ 12.20 (s, 1H), 7.28-7.24 (m, 2H), 7.22-7.20 (m, 1H), 7.15-7.13 (m, 2H), 2.78 (s, 2H), 1.07 (s, 6H). This compound was used in subsequent reaction with out further analysis.

2,2-dimethyl-3-phenylpropanoyl chloride

A solution of 2,2-dimethyl-3-phenylpropanoic acid (0.856 g, 4.8 mmol) in chloroform (6 mL) at 0°C was treated with oxalyl chloride (3.05 g, 24 mmol) and 1 drop of dimethylformamide. The reaction solution was stirred for 1 h at 0°C. The ice bath was removed and the reaction mixture stirred at room temperature over night. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of 2,2-dimethyl-3-phenylpropanoyl chloride. The oil was directly used in the following reaction.

cis-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide

- A solution of *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.23 mmol) in pyridine (2.5 mL) was treated with 2,2-dimethyl-3-phenylpropanoyl chloride (0.120 g, 0.61 mmol). The reaction mixture was stirred for 2 h at room temperature under a nitrogen atmosphere. Saturated sodium bicarbonate solution (10 mL) was added, and the reaction mixture was stirred for 20 min. Solvent was removed under reduced pressure. Dichloromethane and saturated sodium bicarbonate solution was added to the residue. The layers were separated using an Empore extraction cartridge. The organic solvent was removed under reduced pressure. The crude compound was purified by flash chromatography on silica gel, using 10% methanol in dichloromethane as eluent to give 0.085 g (62%) *cis-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide. ¹H NMR (CDCl₃, 400 MHz) δ 8.595-8.574 (m, 1H), 8.372 (s, 1H), 7.985 (s, 1H), 7.292-7.158 (m, 7H), 4.923 (m, 1H), 3.891 (s, 3H), 3.050-3.013 (m, 1H), 2.965 (s, 2H), 2.65-2.55 (m, 5H), 2.440-2.346 (m, 4H), 2.244-2.166 (m, 4H), 1.854-1.823 (m, 3H), 1.688 (m, 3H), 1.334 (s, 6H); HPLC Waters 2690 Alliance HPLC (Symmetry Shield RP₁₈ 3.5 μm, 2.1 x 50 mm; 5%-95% acetonitrile-0.1 M ammonium acetate over 15 min, 0.5 mL/min) R_t 5.517 min (100%).

Example 387 *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide tris-maleate

- A solution of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.250 g, 0.573 mmol) in pyridine (3 mL) at 0°C was treated with 2,2-dimethyl-3-phenylpropanoyl chloride (0.304 g, 1.55 mmol). The reaction mixture was stirred for 10 min at 0°C. The ice bath was removed and the reaction mixture was stirred at room temperature for 5 h. Solvent was removed under reduced pressure to dryness. Dichloromethane (15 mL) and saturated sodium bicarbonate solution (5 mL) were added to the solid.

The layers were separated using an Empore extraction cartridge. The organic solvent was removed under reduced pressure. The crude solid was purified by flash chromatography using 10% methanol in dichloromethane, then 15% (methanol with 5% ammonium hydroxide) in dichloromethane as eluent. The crude solid from the previous purification was recrystallized using ethyl acetate and heptane. The precipitate was filtered to give 0.201 g (59%) of *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide. A hot solution of *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide (0.201, 0.337 mmol) in ethyl acetate was treated with a hot solution of maleic acid (0.117 g, 1.011 mmol) in ethyl acetate. The precipitate was filtered under nitrogen, and dried under high vacuum to give 0.265 g of *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide tri-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.46 (s, 1H), 8.241 (s, 1H), 8.107-8.086 (d, 1H, *J* = 8.4 Hz), 7.248-7.183 (m, 7H), 6.170 (s, 6H), 4.697 (m, 1H), 3.883 (s, 3H), 2.931 (s, 3H), 2.9-2.75 (br. s., 4H), 2.671 (s, 3H), 2.104-1.990 (m, 7H), 1.588-1.5632(m, 2H), 1.226 (s, 7H); HPLC Waters 2690 Alliance HPLC (Symmetry Shield RP₁₈ 3.5 μm, 2.1 x 50 mm; 5%-95% acetonitrile-0.1 M ammonium acetate over 15 min, 0.5 mL/min) R_t 5.413 min (95%).

Example 388 *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(1*S*,2*S*)-2-phenylcyclopropane-1-carboxamide tris-maleate

A solution of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.162 g, 0.371 mmol) in pyridine (2 mL) at 0°C was treated with *trans*-2-phenyl-1-cyclopropylcarbonyl chloride (0.134 g, 0.742 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at 0°C, the ice bath was removed and the reaction mixture stirred at room temperature for 5 h. Additional *trans*-2-phenyl-1-cyclopropylcarbonyl chloride (0.034 g, 0.186 mmol) was added and the reaction mixture stirred for 1 h. The organic layer was removed under reduced pressure, and dichloromethane (15 mL) was then added. The layers were separated using an

Empore extraction cartridge. The organic layer was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using 15% methanol in dichloromethane then 20% methanol in dichloromethane as eluent. The column afforded 0.150 g (70%) of *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(1*S*,2*S*)-2-phenylcyclopropane-1-carboxamide. A hot solution of *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(1*S*,2*S*)-2-phenylcyclopropane-1-carboxamide (0.147, 0.253 mmol) in ethyl acetate was treated with a hot solution of maleic acid (0.088 g, 0.759 mmol) in ethyl acetate. The precipitate formed was filtered under nitrogen and dried under high vacuum to give 0.204 g of *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(1*S*,2*S*)-2-phenylcyclopropane-1-carboxamide tris-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.64 (s, 1H), 8.23-8.21 (m, 2H), 7.33-7.29 (m, 2H), 7.24-7.17 (m, 4H), 6.16 (s, 6H), 4.69-4.66 (m, 1H), 3.90 (s, 3H), 2.90-2.60 (m, 7H), 2.37-2.35 (m, 2H), 2.10-1.99 (m, 8H), 1.70-1.50 (m, 3H), 1.32 (m, 1H); HPLC Waters 2690 Alliance HPLC (Symmetry Shield RP₁₈ 3.5 μm, 2.1 x 50 mm; 5%-95% acetonitrile-0.1 M ammonium acetate over 15 min, 0.5 mL/min) R_t 5.346 min (97%).

20

Examples 389 *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide

25 Example 390 *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-thiophenecarboxamide

Example 391 *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-furamide

30

Amides derived from *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

The commercially available acid chlorides (0.23 mmol) in dichloromethane (100 μ L) were added to *cis* -3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.050 g, 0.115 mmol) in pyridine (800 μ L). The reaction mixtures were stirred over night. The

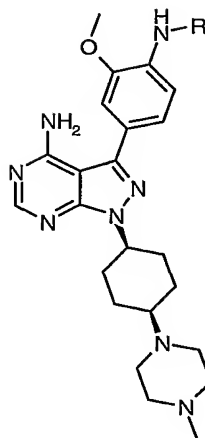
5 reaction mixtures were quenched with 1 N sodium hydroxide solution. Solvent was removed on a Supelco-manifold under vacuum and nitrogen purge. The remaining solids were submitted for preparative HPLC (Hypersil C18, 100x21mm column, 5 μ m, 15-100% Acetonitrile gradient over 8min, total run time - 10min, buffer - 50mM Ammonium Acetate, 25 ml/min). Dichloromethane and 1 N sodium

10 hydroxide solution were added to the solids. The layers were partitioned using an Empore extraction cartridge to give corresponding products. HPLC Perkin Elmer Pecosphere C18, 3 μ M, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3 μ m particle size, 33 x 4.6mm; 100 % 50 mM ammonium

15 Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min)

5

10



Compound Name	R	Qty. (mg)	MH ⁺	R _t (mins)
<i>cis</i>-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1<i>H</i>-pyrazolo[3,4-<i>d</i>]pyrimidin-3-yl}-2-methoxyphenyl)benzo[<i>b</i>]thiophene-2-carboxamide Ex 389		45 (66%)	596.8	3.464
<i>cis</i>-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1<i>H</i>-pyrazolo[3,4-<i>d</i>]pyrimidin-3-yl}-2-methoxyphenyl)-2-thiophenecarboxamide Ex 390		47 (75%)	547.1	2.746
<i>cis</i>-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1<i>H</i>-pyrazolo[3,4-<i>d</i>]pyrimidin-3-yl}-2-methoxyphenyl)-2-furamide Ex 391		36 (59%)	531.3	2.626

Example 392 *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-methyl-3-phenylbutanamide tris-maleate

3-methyl-3-phenylbutanoyl chloride

A solution of 3-methyl-3-phenylbutyric acid (0.508 g, 2.85 mmol) in dichloromethane (10 mL) at -78°C was treated with oxalyl chloride (3.62, 28.5

mmol) and 1 drop of dimethylformamide. The reaction mixture was stirred at -78°C

for 10 min, and dry ice/ acetone bath was removed to stir at room temperature over night. Solvent was removed under reduced pressure, and dried under high vacuum. The product was used directly for subsequent reaction without analysis.

trans-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-
5 *d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-methyl-3-phenylbutanamide tris-maleate

A solution of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.458 mmol) in pyridine (4 mL) at -5°C was treated with a solution of 3-methyl-3-phenylbutanoyl chloride (0.101 g, 0.514 mmol) in dichloromethane (1 mL) drop-
10 wise. The reaction mixture was stirred for 20 min at -5°C, then the dry ice/acetone bath was removed and the reaction mixture stirred at room temperature for 4 h. 1 N sodium hydroxide solution (5 mL) was added and the mixture stirred over night.

Solvent was removed under reduced pressure. The crude solid was dried under high vacuum. Dichloromethane (10 mL) and 1 N sodium hydroxide solution (10 mL)
15 were added. The layers were separated using an Empore extraction cartridge. The organic solvent was removed by blowing nitrogen over the top, to give 0.240 g (88%) of *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-methyl-3-phenylbutanamide.

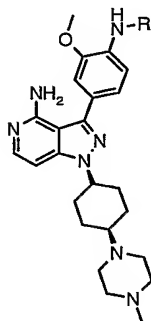
A hot solution of *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-
20 pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-methyl-3-phenylbutanamide (0.240 g, 0.402 mmol) in ethyl acetate and a few drops of ethanol was treated with a hot solution of maleic acid (0.140 g, 1.206 mmol) in ethyl acetate. The precipitated formed was filtered under nitrogen atmosphere, and dried on a lyophilizer to give 0.323 g *trans-N1*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-

25 pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-methyl-3-phenylbutanamide tris-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.807 (s, 1H), 8.226 (s, 1H), 8.109-8.088 (d, 1H, *J* = 8.4 Hz), 7.489-7.470 (d, 2H, *J* = 7.6 Hz), 7.345-7.306 (m, 2H), 7.213-7.134 (m, 3H), 6.151 (s, 5H), 4.680 (m, 1H), 3.836 (s, 3H), 3.3 (br. s., 7H), 2.655 (s, 3H), 2.541 (s, 4H), 2.085-1.989 (m, 6H), 1.574-1.551 (m, 2H), 1.431 (s, 30 6H); HPLC Waters 2690 Alliance HPLC (Symmetry Shield RP₁₈ 3.5 μm, 2.1 x 50 mm; 5%-95% acetonitrile-0.1 M ammonium acetate over 15 min, 0.5 mL/min) R_t 5.407 min (99%).

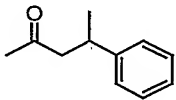
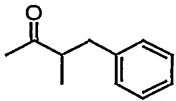
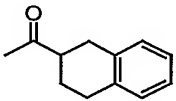
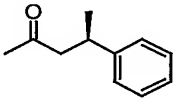
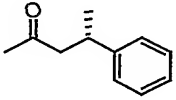
Examples 393- 397 Amides derived from *cis* -3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

5 Representative procedure:

To the appropriate carboxylic acid (0.46 mmol) in dichloromethane (1.4 mL) was added oxalyl chloride (0.4 mL, 4.6 mmol) and DMF (1 drop). The vials were septum capped and a small bore needle inserted in each cap to relieve pressure. The vials were shaken overnight on a J-Kem shaker. 50% of the solution was separated and the excess oxalyl chloride and dichloromethane was then removed on a 12-port Supelco manifold under vacuum with nitrogen bleed. The crude acid chloride (0.23 mmol) was added to *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (50 mg, 0.11 mmol) in dry pyridine (0.6 mL) and stirred at room temperature overnight. The resulting solutions were submitted directly to purification by preparative HPLC (Hypersil BSD C18, 5 μ m, 100x21mm, 0%-100% acetonitrile/0.05M ammonium acetate over 10 min, 25.0 mL/min). The resulting products were further purified by partitioning between dichloromethane (4 ml) and 1.0 N sodium hydroxide (2 ml) and passing through an EmporeTM high performance extraction disk cartridge (C18-SD octadecyl) to give the corresponding products. The compounds are detailed overleaf with corresponding LCMS (Micromass- Column: Pecosphere, C18, 3 μ m, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5) , 3.5 mL/min.) data.



Compound Name	R	Qty. (mg)	MH ⁺	R _t (mins)
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N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-3-phenylbutanamide Ex 393		25	583.4	2.76
N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-2-methyl-3-phenylpropanamide Ex 394		20	583.4	2.76
N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1,2,3,4-tetrahydro-2-naphthalenecarboxamide Ex 395		30	595.4	2.97
N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-(3R)-3-phenylbutanamide Ex 396		14	583.4	2.85
N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-(3S)-3-phenylbutanamide Ex 397		13	583.4	2.78

Example 398 *cis*-N4-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3,5-dimethyl-4-isoxazolecarboxamide

- 5 a) *cis*-*tert*-Butyl N-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate
cis-3-Iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (10 g, 22.66 mmol), *tert*-butyl N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (9.49 g, 27.17 mmol),
10 palladium tetrakis(triphenylphosphine) (1.57 g, 1.36mmol) and sodium carbonate (5.76 g, 54.38 mmol) were mixed with ethylene glycol dimethyl ether (180mL) and water (90 mL). The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine,
15 dried over MgSO₄, filtered and evaporated. The residue was purified by preparative thin layer column chromatography using dichloromethane/methanol (80:20) as

mobile phase to give *cis-tert-butyl N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate (10.859 g, 89%). ¹H NMR (DMSO-*d*₆) δ 1.49 (s, 9H), 1.58 (m, 2H), 1.71 (m, 2H), 2.08 (m, 2H), 2.17 (s, 3H), 2.45 (m, 4H), 2.38 (m, 4H), 2.45 (m, 3H), 3.87 (s, 3H), 4.80 (m, 1H), 7.22 (m, 2H), 7.91 (d, J=8.14, 1H), 8.04 (s, 1H), 8.22 (s, 1H).

b) *cis*-3-(4-Amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of trifluoroacetic acid/dichloromethane (20:80, 200 mL) was added to a solution of *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate (10.85 g, 20.24 mmol) in dichloromethane (100 mL) at 0°C. 2 hours later, the ice-bath was removed and the solvents were evaporated and the residue was dissolved in dichloromethane. Sodium hydroxide (1.0N) was added to adjust the pH to about 10. The solid formed upon removal of organic solvent was collected by filtration to give *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (8.84g, 100%). ¹H NMR (CDCl₃) δ 1.65 (m, 2H), 1.83 (m, 2H), 2.18 (m, 2H), 2.31 (s, 3H), 2.35-2.60 (m, 11H), 3.90 (s, 3H), 4.00 (bs, 2H), 4.89 (m, 1H), 5.61 (bs, 2H), 6.83 (d, J=7.78Hz, 1H), 7.12 (m, 2H), 8.35 (s, 1H).

c) *cis-N*4-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3,5-dimethyl-4-isoxazolecarboxamide

3,5-Dimethyl-4-isoxazolecarbonyl chloride (22 mg, 0.137 mmol) was added to a solution of *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (30 mg, 0.067 mmol) in pyridine (0.5 mL). After 5 hours, the solvent was evaporated and the residue was re-crystallized from DMSO to give *cis-N*4-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3,5-dimethyl-4-isoxazolecarboxamide (33 mg, 87%). ¹H NMR (DMSO-*d*₆) δ 1.91 (m, 2H), 2.24 (m, 2H), 2.36 (m, 2H), 2.41 (s, 3H), 2.63 (s, 3H), 2.77 (m, 3H), 3.17 (s, 3H), 3.37 (bm, 8H), 3.95 (s, 3H), 4.95 (m, 1H), 7.37 (m, 2H), 8.17 (d, J=8.17, 1H), 8.30 (s, 1H), 9.26 (s, 1H). LC/MS (Micromass-Column: Pecosphere, C18, 3 μm, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia

acetate buffer, pH 4.5), 3.5 mL/min.), $MH^+ = 560.2$, $R_t = 2.44$ min.

Example 399 *cis-N3*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-5-methyl-3-isoxazolecarboxamide

5-Methyl-3-isoxazolecarbonyl chloride (20 mg, 0.137 mmol) was added to a solution of *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (30 mg, 0.067 mmol) in pyridine (0.5 mL). After 5 hours, the solvent was evaporated and the residue was purified by preparative HPLC (Hypersil BSD C18, 5 μ m, 100x21mm, 0%-100% acetonitrile/0.05M ammonium acetate over 10 min, 25.0 mL/min). The resulting products were further purified by partitioning between dichloromethane (4 ml) and 1.0 N sodium hydroxide (2 ml) and passing through an EmporeTM high performance extraction disk cartridge (C18-SD octadecyl) to give *cis-N3*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-5-methyl-3-isoxazolecarboxamide (14 mg, 38%). ¹H NMR (DMSO-*d*₆) δ 1.81 (m, 2H), 2.14 (m, 2H), 2.35 (m, 2H), 2.53 (s, 3H), 2.76 (m, 3H), 3.37 (bm, 8H), 3.99 (s, 3H), 4.93 (m, 1H), 6.74 (s, 1H), 7.36 (m, 2H), 8.26 (m, 1H), 9.48 (s, 1H); LCMS (Finigan- Column: Pecosphere, C18, 3 μ m, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 3.0 mL/min.): $MH^+ = 546.4$, $R_t = 1.82$ min.

Example 400 *cis-N1*-[(2*R*)-2-Phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide, dimaleate salt

cis-N1-[(2*R*)-2-Phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide (100 mg, 0.172 mmol) was dissolved in hot ethyl acetate (12 mL) and maleic acid (60 mg, 0.515 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature for 5 hours. The solid was collected by filtration to give *cis-N1*-[(2*R*)-2-phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide, dimaleate salt (117 mg, 87%). ¹H NMR (DMSO-*d*₆) δ 1.25 (d,

J=6.96, 3H), 1.73 (m, 42H), 2.09 (m, 2H), 2.26 (m, 2H), 2.71 (s, 3H), 2.74 (m, 2H), 2.85-3.70 (bm, 7H), 3.89 (s, 3H), 4.85 (m, 1H), 6.14 (s, 4H), 7.20 (m, 3H), 7.31(d, J=4.33, 4H), 8.12 (d, J=8.17 Hz, 1H), 8.24 (s, 1H), 9.20 (s, 1H). LC/MS (Finigan-Column: Pecosphere, C18, 3 μ m, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 3.0 mL/min.): MH⁺= 583.4 R_t=2.14 min.

Example 401 *trans*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)benzo[b]furan-2-carboxamide, trimaleate salt

a) *trans*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)benzo[b]furan-2-carboxamide

To benzo[b]furan-2-carboxylic acid (0.743g, 4.58 mmol) in dichloromethane (14 mL) was added oxalyl chloride (4 mL, 45.8 mmol) and DMF (1 drop). The reaction mixture was stirred overnight. Solvent was evaporated and the residue was dissolved in Dichloromethane (5 mL). Half of the dichloromethane solution (2.5 mL) was added to a solution of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.50 g, 1.145 mmol) in pyridine (6 mL) at 0°C. After 30 minutes, the solid as collected by filtration. Water was then added to the solid and the pH of the solution was adjusted to 10 with sodium hydroxide (1.0N). The aqueous was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (80:20) as mobile phase to give *trans*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)benzo[b]furan-2-carboxamide (0.497 g, 75%).¹H NMR (DMSO-*d*₆) δ 1.49 (m, 2H), 2.01 (m, 6H), 2.15 (s, 3H), 2.40 (m, 3H), 2.51 (m, 4H), 4.00 (s, 3H), 4.66 (m, 1H), 7.31 (m, 1H), 7.39 (m, 2H), 7.54 (m, 1H), 7.81 (m, 3H), 8.24 (m, 1H), 9.50 (s, 1H).

b) *trans*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)benzo[b]furan-2-carboxamide, trimaleate salt

trans-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)benzo[b]furan-2-carboxamide

(497 mg, 0.855 mmol) was dissolved in hot ethyl acetate (56 mL) and maleic acid (298mg, 2.566 mmol) in hot ethyl acetate (5 mL) was added. The reaction mixture was stirred at room temperature for 5 hours. The solid was collected by filtration to give *trans*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)benzo[*b*]furan-2-carboxamide, trimaleate salt (117 mg, 92%). ¹H NMR (DMSO-*d*₆) δ 1.60 (m, 2H), 2.09 (m, 6H), 2.68 (s, 3H), 2.82-3.17 (bm, 9H), 4.00 (s, 3H), 4.69 (m, 1H), 6.16 (s, 6H), 7.30-7.42 (m, 3H), 7.54 (m, 1H), 7.76-7.85 (m, 3H), 8.25 (m, 2H), 9.51 (s, 1H); LCMS (Finigan- Column: Pecosphere, C18, 3 um, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 3.0 mL/min.): MH⁺=581.4, R_t=2.12 min.

Example 402 *trans*-N1-[(2*R*)-2-Phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide, trimaleate salt

a) *trans*-N1-[(2*R*)-2-Phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide

To (3*R*)-3-phenylbutanoic acid (376 mg, 2.29 mmol) in dichloromethane (7 mL) was added oxalyl chloride (2 mL, 22.9 mmol) and DMF (1 drop). The reaction mixture was stirred overnight. Solvent was evaporated and the residue was dissolved in dichloromethane (3 mL). The dichloromethane solution was added to a solution of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (448 mg, 1.026 mmol) in pyridine (6 mL) at 0°C. After 2 hours, the reaction mixture was poured to ethyl acetate (60 mL) and the solid as collected by filtration. Water was then added to the solid and the pH of the solution was adjusted to 10 with sodium hydroxide (1.0N). The aqueous was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (80:20) as mobile phase to give *trans*-N1-[(2*R*)-2-phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide (383 mg, 64%). ¹H NMR (CDCl₃) δ 1.40

(d, J=6.96, 3H), 1.57 (m, 2H), 2.08-2.21 (m, 6H), 2.30 (s, 3H), 2.50 (m, 5H), 2.63-2.74 (m, 6H), 3.40 (m, 1H), 3.88 (s, 3H), 4.74(m, 1H), 5.69 (bs, 2H), 7.16-7.34 (m, 7H), 7.66 (s, 1H), 8.34 (s, 1H), 8.49 (d, J=8.21, 1H).

b) *trans*-N1-[(2R)-2-Phenylpropyl]-4-{4-amino-1-[4-(4-

5 methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide, trimaleate salt

trans-N1-[(2R)-2-Phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide (383 mg, 0.657 mmol)

was dissolved in hot ethyl acetate (42 mL) and maleic acid (229mg, 1.971 mmol) in

10 hot ethyl acetate (5 mL) was added. The reaction mixture was stirred at room

temperature for 5 hours. The solid was collected by filtration to give *trans*-N1-[(2R)-2-phenylpropyl]-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxybenzamide (571 mg, 93%). ¹H NMR (DMSO-*d*₆) δ 1.25 (d, J=6.95, 3H), 1.57 (m, 2H), 2.03 (m, 6H), 2.60-3.40 (bm,

15 18H), 3.89 (s, 3H), 4.67(m, 1H), 6.16 (s, 6H), 7.20 (m, 3H), 7.31 (d, J=4.37 Hz, 4H), 8.14 (d, J=8.22 Hz, 1H), 8.23 (s, 1H), 9.18 (s, 1H). LC/MS (Micromass- Column: Pecosphere, C18, 3 um, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 3.5 mL/min.): MH⁺=583.2, R_t=2.89 min.

20

Example 403 *tert*-Butyl N-{4-[4-amino-1-(1-(1-methylpiperidin-4-yl)-piperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate

a) *tert*-Butyl 4-hydroxy-1-piperidinecarboxylate

Sodium borohydride (3.8 g, 100.4 mmol) was added in portions to a solution of *tert*-butyl 4-oxo-1-piperidinecarboxylate (20 g, 100.4 mmol) in methanol (600 mL) at 0°C. After 15 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 3 hours. Sodium hydroxide (1.0 N, 100 mL) was added and the organic solvent was evaporated. The aqueous was extracted with ether four times. The combined organic layer was washed with water then

30 brine, dried over MgSO₄, filtered and evaporated to give *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (20.48 g, 100%). ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.63 (m, 2H), 1.87 (m, 2H), 3.03 (m, 2H), 3.83 (m, 3H).

b) *tert*-Butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

3-Iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (10 g, 38.3 mmol), *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (16.96 g, 84.2 mmol) and triphenylphosphine (20.09 g, 76.0 mmol) were suspended in tetrahydrofuran (425 mL). The reaction mixture was cooled in an ice-water bath and diethyl azodicarboxylate (12.09 mL, 76.0 mmol) was added dropwise. 10 minutes later, the reaction mixture was allowed to warm up to room temperature. 5 hours later, solvent was removed under reduced pressure and dichloromethane (65 mL) was added with heating. The solid was filtered and washed with dichloromethane (20 mL). The solid was further washed with ethyl acetate (5x20 mL) to give a mixture of diethyl 1,2-hydrazinedicarboxylate and *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (1:1, 14.98 g, 63%) which was used without further purification. ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.95 (m, 2H), 2.20 (m, 2H), 2.92 (m, 2H), 4.23 (m, 2H), 4.84 (m, 1H), 8.31 (s, 1H).

c) 3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of trifluoroacetic acid/dichloromethane (20:80, 250 mL) was added to a solution of *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (10.72 g, 24.1 mmol) in dichloromethane (100 mL) at 0°C. 15 minutes later, the ice-bath was removed and the reaction mixture was stirred at room temperature for 5 hours. The solvents were evaporated and the residue was dissolved in dichloromethane. Hydrochloric acid (5.0N) was added and the aqueous layer was washed with dichloromethane three times. Sodium hydroxide (50%) was added to adjust the pH to about 10. The suspension was lyophilized to reduce the volume to one third of the original volume. The solid was collected by filtration to give 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (8.109 g, 97%). ¹H NMR (CDCl₃) δ 1.81 (m, 2H), 1.99 (m, 2H), 2.65 (m, 2H), 3.07 (m, 2H), 4.68 (m, 1H), 8.19 (s, 1H).

d) 3-Iodo-1-[1-(1-methylpiperidin-4-yl)]-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.00 g, 5.81 mmol), 1-methyl-4-piperidone (2.14 mL, 17.42 mmol), sodium

triacetoxyborohydride (2.45 g, 11.62 mmol) and glacial acetic acid (1.05g, 17.42 mmol) were mixed with 1,2-dichloroethane (75 mL). The reaction mixture was stirred at room temperature for 6 hours and saturated sodium bicarbonate solution was added to adjust the pH to about 9. The solid was collected by filtration to give
5 3-Iodo-1-[1-(1-methylpiperidin-4-yl)]-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.39 g, 93%). ¹H NMR (DMSO-*d*₆) δ 1.52 (m, 2H), 1.75 (m, 2H), 1.87 (m, 2H), 2.05 (m, 4H), 2.24 (s, 3H), 2.28 (m, 3H), 2.91 (m, 2H), 3.00 (m, 2H), 4.55 (m, 1H), 8.18 (s, 1H).

e) *tert*-Butyl *N*-{4-[4-amino-1-[1-(1-methylpiperidin-4-yl)]-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl} carbamate
10 3-Iodo-1-[1-(1-methylpiperidin-4-yl)]-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.39 g, 5.41 mmol), *tert*-butyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (2.08 g, 5.96 mmol), palladium tetrakis(triphenylphosphine) (0.375 g, 0.32 mmol) and sodium carbonate
15 (1.38 g, 13.00 mmol) were mixed with ethylene glycol dimethyl ether (80 mL) and water (40 mL). The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash
20 column chromatography using dichloromethane/methanol/ammonium hydroxide (95:5:0.5) as mobile phase to give *tert*-butyl *N*-{4-[4-amino-1-[1-(1-methylpiperidin-4-yl)]-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl} carbamate (1.67 g, 57%). ¹H NMR (DMSO-*d*₆) δ 1.48 (m, 11H), 1.71 (m, 2H) 1.86 (m, 4H), 2.14 (s, 3H), 2.18 (m, 3H), 2.32 (m, 2H), 2.80 (m, 2H),
25 3.89 (s, 3H), 4.64 (m, 1H), 7.22 (m, 2H), 7.91 (d, J=8.12, 1H), 8.03 (s, 1H), 8.21 (s, 1H).

Example 404 3-{4-[(2-Furylmethyl)amino]-3-methoxyphenyl}-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
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a) 3-(4-Amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of trifluoroacetic acid/dichloromethane (20:80, 28 mL) was added to a solution of *tert*-butyl *N*-{4-[4-amino-1-[1-(1-methylpiperidin-4-yl)-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate (0.914 g, 1.70 mmol) in dichloromethane (5 mL) at 0°C. After 15 minutes, the ice-bath was removed and the reaction mixture was stirred at room temperature for 5 hours. Solvents were then evaporated and the residue was dissolved in dichloromethane. Saturated sodium bicarbonate was added to adjust the pH to about 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated give 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.726 g, 97%). ¹H NMR (CDCl₃) δ 1.67 (m, 2H) 1.83 (m, 4H), 2.00 (m, 2H), 2.27 (s, 3H), 2.39 (m, 5H), 2.91 (m, 2H), 3.08 (m, 2H), 3.92 (s, 3H), 3.99 (m, 2h), 4.73 (m, 1H), 5.56 (bs, 2H), 6.82 (d, J=7.87, 1H), 7.08 (d, J=7.84, 1H), 7.13 (s, 1H), 8.34 (s, 1H).

b) 3-{4-[(2-Furylmethyl)amino]-3-methoxyphenyl}-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

3-(4-Amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)-piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (100 mg, 0.229 mmol), 2-furaldehyde (0.027 mL, 0.321 mmol), sodium triacetoxyborohydride (193 mg, 0.916 mmol) and glacial acetic acid (55 mg, 0.916 mmol) were mixed with 1,2-dichloroethane (5 mL). The reaction mixture was stirred at room temperature overnight. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated.

The residue was purified by flash column chromatography using dichloromethane/methanol/ammonium hydroxide (95:5:0.2) as mobile phase to give 3-{4-[(2-furylmethyl)amino]-3-methoxyphenyl}-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (57 mg, 48%). ¹H NMR (DMSO-*d*₆) δ 1.45 (m, 2H), 1.71 (m, 2H), 1.87 (m, 4H), 2.14 (s, 3H), 2.28 (m, 5H), 2.80 (m, 2H), 3.01 (m, 2H), 3.86 (s, 1H), 4.37 (d, J=3.13, 1H), 6.76 (d, J=8.62, 1H), 7.07 (m, 2H), 7.57 (s, 1H), 8.19 (s, 1H). LCMS (Finigan- Column: Pecosphere, C18, 3 um, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4 min. (B: acetonitrile, A: 50

mM ammonia acetate buffer, pH 4.5), 3.0 mL/min.): MH^+ 517.3, R_t =2.28 min.

Example 405 *N1*-{4-[4-Amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenylcyclopropane-1-carboxamide, dimaleate salt

a) *N1*-{4-[4-Amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenylcyclopropane-1-carboxamide

trans-2-Phenyl-1-cyclopropanecarbonyl chloride (42 mg, 0.231 mmol) was added to a solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (100 mg, 0.229 mmol) in pyridine (1.0 mL). After 5 hours, the solvent was evaporated and the residue was purified by flash column chromatography to give *N1*-{4-[4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenylcyclopropane-1-carboxamide (80 mg, 60%). 1H NMR ($CDCl_3$) δ 1.42 (m, 1H), 1.77 (m, 2H), 1.85 (m, 2H), 2.06 (m, 3H), 2.36-2.45 (m, 8H), 2.62 (m, 1H), 3.00 (m, 2H), 3.10 (m, 2H), 3.96 (s, 3H), 4.75 (m, 1H), 5.54 (bs, 2H), 7.14-7.33 (m, 7H), 8.10 (s, 1H), 8.36 (s, 1H), 8.54 (d, J =8.50, 1H). LCMS (Finigan- Column: Pecosphere, C18, 3 μ m, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 3.0 mL/min.): MH^+ =581.4, R_t =1.77 min.

b) *N1*-{4-[4-Amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenylcyclopropane-1-carboxamide, dimaleate salt

N1-{4-[4-Amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenylcyclopropane-1-carboxamide (75 mg, 0.129 mmol) was dissolved in ethanol (2 mL) and maleic acid (45 mg, 0.387 mmol) in ethanol (1 mL) was added. The reaction mixture was stirred at room temperature for 5 hours. The solvent was removed and ethyl acetate was added and the solid was collected by filtration to give *N1*-{4-[4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenylcyclopropane-1-carboxamide, dimaleate salt (75 mg). 1H NMR ($DMSO-d_6$) δ 1.17 (m, 1H), 1.32 (m, 2H), 1.48 (m, 2H), 1.48, (m,

2H), 2.19 (m, 4H), 2.37 (M, 1H), 2.46 (m, 1H), 2.59 (m, 1H), 2.78 (s, 3H), 2.98-3.52 (bm, 9H), 3.90 (s, 3H), 5.02 (m, 1H), 6.08 (s, 4H), 7.17-7.33 (m, 7H), 8.25 (m, 2H), 9.65 (s, 1H). LCMS (Finigan- Column: Pecosphere, C18, 3 um, 33x4.6 mm.

Eluents: 0% B/A to 100% B/A in 4 min. (B: acetonitrile, A: 50 mM ammonia

5 acetate buffer, pH 4.5), 3.0 mL/min.): MH^+ =581.4, R_t =1.77 min.

Examples 406 and 407

Amides derived from *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

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Representative procedure:

To the appropriate carboxylic acid (0.46 mmol) in dichloromethane (1.5 ml) was added oxalyl chloride (400 μ l, 0.2 mmol) and DMF (1 drop). The vials were septum capped and a small bore needle inserted in each cap to relieve pressure. The vials

15 were shaken overnight on a J-Kem shaker. 50% of the solution was separated and the excess oxalyl chloride and dichloromethane was then removed on a 12-port Supelco manifold under vacuum with nitrogen bleed. The crude acid chloride (0.23 mmol) was added to *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-

methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (40 mg, 0.09

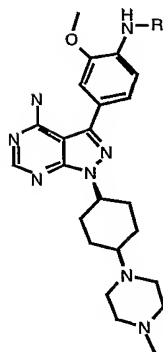
20 mmol) in dry pyridine (800 μ l) and stirred at room temperature. The resulting solutions were submitted directly to purification by preparative HPLC (Hypersil BSD C18, 5 um, 100x21mm, 0%-100% acetonitrile/0.05M ammonium acetate over 10 min, 25.0 mL/min). The resulting products were further purified by partitioning

between dichloromethane (4 ml) and 1.0 N sodium hydroxide (2 ml) and passing

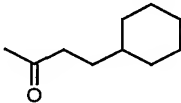
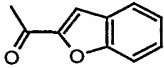
25 through an EmporeTM high performance extraction disk cartridge (C18-SD octadecyl) to give the corresponding products. The compounds are detailed overleaf with corresponding LCMS (Micromass- Column: Pecosphere, C18, 3 um, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5) , 3.5 mL/min.) data.

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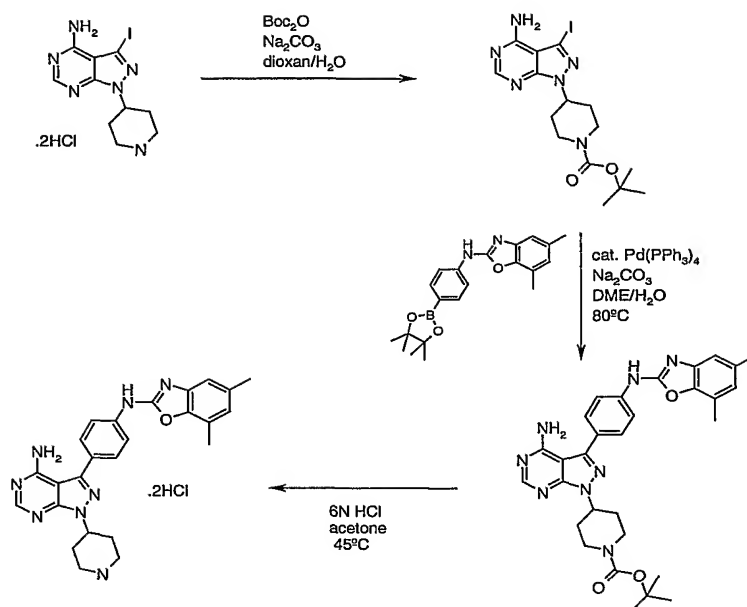
Compound Name	R	Qty. (mg)	MH ⁺	R _t (mins)
N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-y}-2-methoxyphenyl)-3-cyclohexylpropanamide Ex 406		11	575.3	3.3
N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide Ex 407		20	581.3	2.98

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Example 408 N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine dihydrochloride

15

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a) tert-Butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboxylate

Di-tert-butyl dicarbonate (0.287 g, 1.32 mmol) was added to a mixture of 3-iodo-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride (0.50 g, 1.20 mmol) and sodium carbonate (0.445 g, 4.20 mmol) in dioxane (10 mL) and water (10 mL) and the reaction was stirred for 18 h. Dichloromethane (100 mL) was added and the organic layer was washed with water (30 mL) and brine (30 mL), dried (Na₂SO₄) and concentrated in vacuo to afford tert-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboxylate as a light yellow solid (0.524 g, 98 %); RP-HPLC 12.227 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); m/z (MH⁺) = 445.1.

b) tert-Butyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboxylate

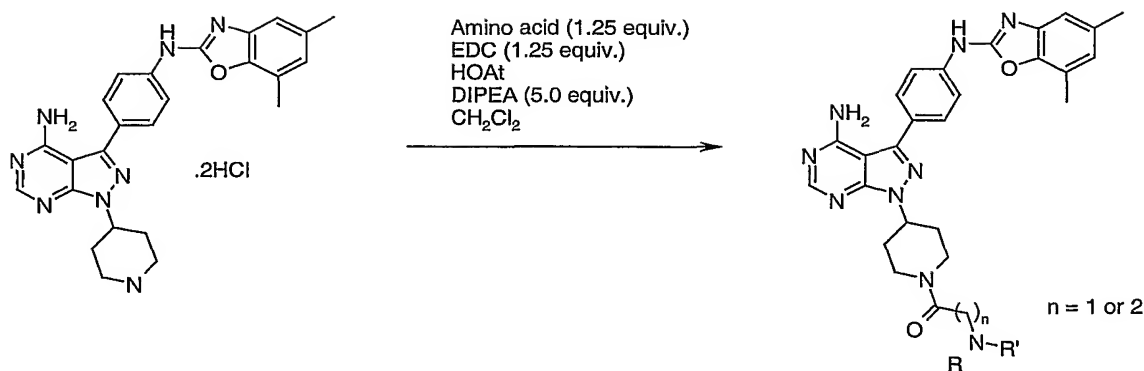
tert-Butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboxylate (524 mg, 1.18 mmol) was dissolved in ethylene glycol dimethylether (50 mL) and water (10 mL). N-(1,3-benzoxazol-2-yl)-N-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (537 mg, 1.47 mmol), palladium tetrakis(triphenyl)phosphine (68 mg, 0.059 mmol) and sodium carbonate (313 mg, 2.95 mmol) were added and the reaction was heated at 80 °C for 19 hours. Additional boronate (188 mg, 0.515 mmol) and palladium

tetrakis(triphenyl)phosphine (27 mg, 0.024 mmol) were added and the reaction was heated at 80 °C for a further 23 hours. The reaction was concentrated under reduced pressure. The remaining residue was partitioned between dichloromethane (100 mL) and water (100 mL). The organic layer was dried (Na₂SO₄) then concentrated under reduced pressure to yield an orange oil (1.4 g). Purification by chromatography over silica gel using a 2 : 1 to 9 : 1 ethyl acetate : heptane gradient followed by a 2% to 5% methanol in dichloromethane gradient afforded tert-butyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboxylate as a tan solid (577 mg, 85%); RP-HPLC 17.090 min, 98% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); m/z (MH⁺) = 555.2.

c). N₂-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine dihydrochloride

tert-Butyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboxylate (142 mg, 0.256 mmol) was dissolved in acetone (7 mL) and 6N aqueous hydrochloric acid (1.4 mL). The reaction was then heated at 45 °C which yielded a precipitate. After 2.5 hours, the precipitate was collected by vacuum filtration, washed with a minimal amount of acetone and dried on the lyophilizer to N₂-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine dihydrochloride as an orange solid (130 mg, 96%); -HPLC 10.436 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); m/z (MH⁺) = 455.3.

Examples 409-416 General synthesis of piperidine amide analogs of N₂-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine.



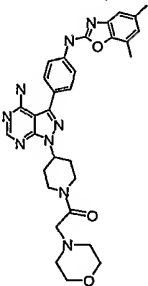
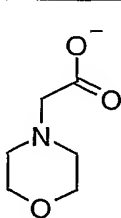
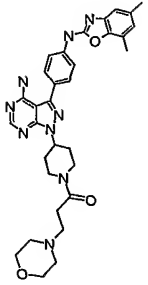
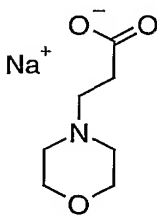
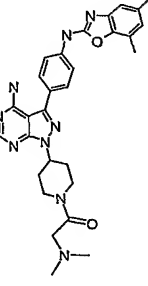
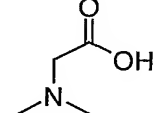
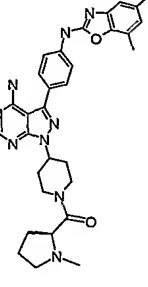
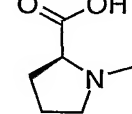
Each 20 mL scintillation vial was charged with N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine dihydrochloride (45 mg, 0.085 mmol), the N-unprotected or N-protected amino acid (1.25 equivalents), 1-hydroxy-7-azabenzotriazole (12 mg, 0.085 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20 mg, 1.06 mmol), N-ethyl-N,N-diisopropylamine (74 μ L, 0.425 mmol) and dichloromethane (5 mL). The reaction was oscillated at ambient temperature for 2.5 days. For the reactions which did not reached completion, additional N-ethyl-N,N-diisopropylamine (15 μ L, 0.085 mmol) and) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8 mg, 0.0425 mmol) were added. In addition for the reactions which had low solubility, DMF (1 mL) was also added. The reactions were concentrated *in vacuo*, dissolved in dichloromethane (2 mL), washed with brine (2 mL) and the layers were separated by passing through an Empore cartridge (6 mL). The organic layer was concentrated under reduced pressure. For products with less than 80% purity, the samples were purified by RP-HPLC (Waters PrepLC 4000, flow rate: 10 mL/min. λ = 254 nm Gradient: 15% to 35% acetonitrile/0.1M aqueous ammonium acetate gradient over 40 minutes; Deltapak C18, 300Å, 15 μ m, 40 x 100 mm column). The *N-tert*-butoxycarbonyl protected products (0.11 mmol) were deprotected by subjecting to 6N HCl (0.7 mL) and acetone (3.5 mL) at 45°C for 4.5 h. The acetone was removed under reduced pressure and the products were purified by RP-HPLC (Waters PrepLC 4000, flow rate: 10 mL/min. λ = 254 nm Gradient: 15% to 35% acetonitrile/0.1M aqueous ammonium acetate gradient over 40 minutes; Deltapak C18, 300Å, 15 μ m, 40 x 100 mm column).

The *N*-(9-fluorenylmethoxycarbonyl) protected products (0.126 mmol) were deprotected by subjecting them to piperidine (0.4 mL) in DMF (1.6 ml) at room temperature for 3.5 h. The products were then purified by RP-HPLC (Waters PrepLC 4000, flow rate: 10 mL/min. λ = 254 nm Gradient: 15% to 35%

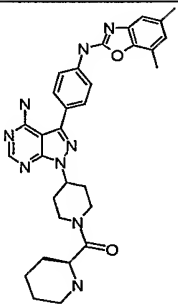
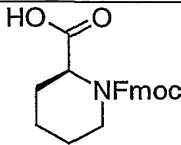
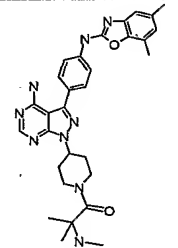
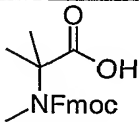
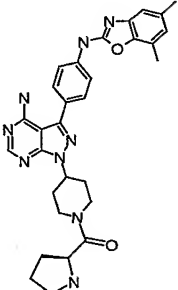
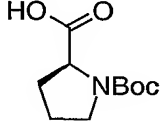
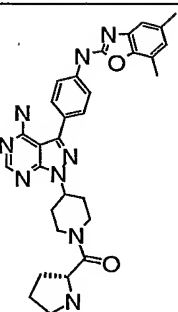
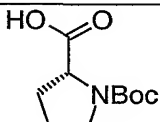
- 5 acetonitrile/0.1M aqueous ammonium acetate gradient over 40 minutes; Deltapak C18, 300Å; 15 μ m, 40 x 100 mm column).

The products were analyzed by RP-HPLC (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column) and mass spectrometry to

- 10 characterize the following compounds:

Example No.	Structure	Starting amino acid	m/z (MH ⁺)	HPLC Rt (min)	Purity
409			582.2	11.394	96%
410			596.3	11.104	91%
411			540.2	9.287	93%
412			566.2	11.160	100%

Example	Structure	Starting amino acid	m/z	HPLC Rt	Purity
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No.			(MH ⁺)	(min)	
413			566.2	11.139	100%
414			554.3	11.035	93%
415			552.2	11.051	100%
416			551.9	11.027	100%

Example 417 cis-4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl 2,3-dichloro-1-benzenesulfonate

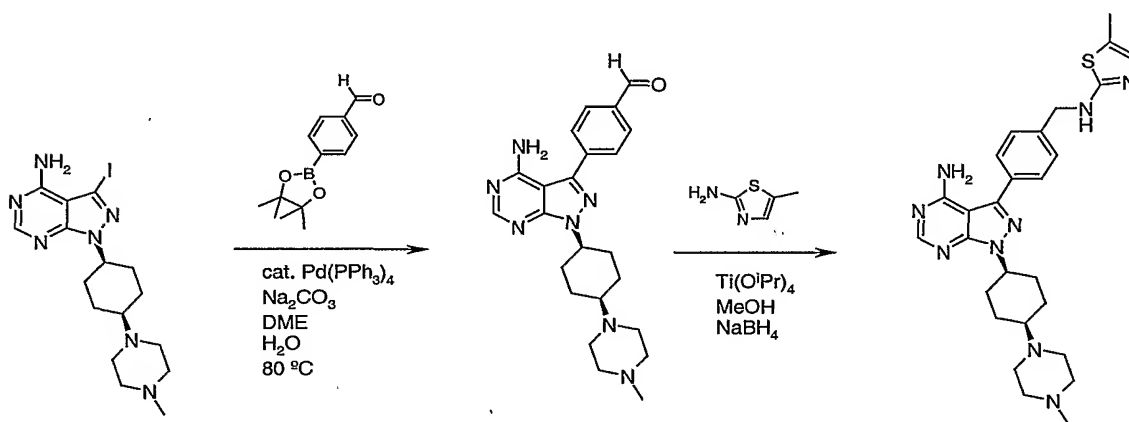
5

A solution containing cis-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenol (100 mg, 0.245 mmol), 2,3-dichlorobenzenesulfonyl chloride (180 mg, 0.735 mmol) and triethylamine (0.34

mL, 2.45 mmol) in dichloromethane (8 mL) was stirred at ambient temperature for 17 h. Additional dichloromethane was added (20 mL) and the reaction was washed with brine (10 mL), saturated aqueous NaHCO₃ (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford cis-4-{4-amino-1-[4-(4-

5 methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl 2,3-dichloro-1-benzenesulfonate as a white solid (135 mg, 90%); RP-HPLC 11.787 min, 97 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); m/z (MH⁺) = 616.2.

10



Example 418 N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-

15 pyrazolo[3,4-d]pyrimidin-3-yl}benzyl)-5-methyl-1,3-thiazol-2-amine
 (a) cis-4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-
 d]pyrimidin-3-yl}benzaldehyde.

A mixture of cis-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-
 d]pyrimidin-4-ylamine (5.0 g, 11.33 mmol), 4-formylphenyl boronic acid (2.55 g,
 20 16.98 mmol), palladium tetrakis(triphenylphosphine) (0.47 g, 0.4 mmol), and sodium
 carbonate (3.002 g, 28.32 mmol) in ethylene glycol dimethylether (170 mL) and
 water (30 mL) was heated at 80 °C for 18 h. Additional boronate (1.567 equiv.) and
 catalyst (0.0135 equiv.) were added and the reaction continued for a further 40 h.
 The reaction was cooled to ambient temperature and concentrated *in vacuo*. The
 25 residues were partitioned between ethyl acetate (300 mL) and water (200 mL). The
 resulting precipitate was collected by filtration and dried on the lyophiliser to afford

cis-4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}benzaldehyde as a light brown solid (2.1 g, 43 %); RP-HPLC 7.003 min, 98 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (DMSO- d_6 , 400 MHz) δ 1.60 (2H, *br t*), 1.72 (2H, *m*), 2.06 (2H, *m*), 2.17 (3H, *s*), 2.27 (3H, *m*), 2.35-2.50 (6H, *m*), 3.39 (2H, *m*), 4.84 (1H, *m*), 7.88 (2H, *d*), 8.07 (2H, *d*), 8.26 (1H, *s*), and 10.11 (1H, *s*)

b) N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}benzyl)-5-methyl-1,3-thiazol-2-amine

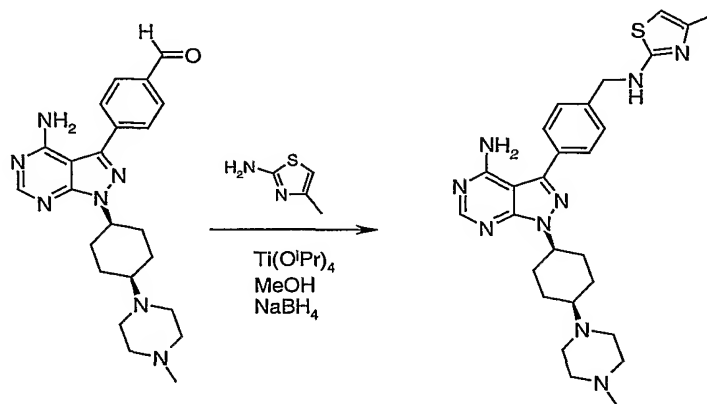
- 10 A slurry containing cis-4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}benzaldehyde (100 mg, 0.24 mmol) and 2-amino-5-methylthiazole (33 mg, 0.29 mmol) in titanium isopropoxide (0.48 mL) was stirred at room temperature for 4h. Methanol (2 mL) was added followed by careful addition of sodium borohydride (13.5 mg, 0.36 mmol). After 10 min. the
- 15 effervescence subsided and the reaction was quenched with aqueous sodium hydroxide (0.1 N, 10 mL). The resulting mixture was allowed to stand overnight then filtered through a celite pad using additional methanol (approx. 10 mL). The filtrate was evaporated to dryness then dissolved in dichloromethane (50 mL) and washed with brine (50 mL). The aqueous layer was extracted further with
- 20 dichloromethane (3 x 50 mL) and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification by RP-HPLC (Pecosphere, C18, 3 μ m, 33 x 4.6 mm column, 0% to 100% acetonitrile in 50mM ammonium acetate, buffered to pH 4.5, at 3.5 mL/min) afforded 2 fractions. The first fraction contained (4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-cyclopenta[d]pyrimidin-5-
- 25 yl}phenyl)methanol (5 mg, 5 %); RP-HPLC 6.261 min, 82 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); m/z (MH^+) = 422.1.

The second fraction afforded N2-(4-{4-Amino-1-[4-(4-

- 30 methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}benzyl)-5-methyl-1,3-thiazol-2-amine (4 mg, 3 %); RP-HPLC 8.344 min, 100 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at

1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (DMSO- d_6 , 400 MHz) δ 1.59 (2H, *br t*), 1.70 (2H, *m*), 2.07 (2H, *m*), 2.10-2.50 (9H, *m*), 2.16 (3H, *s*), 2.54 (3H, *s*), 3.29 (2H, *m*), 4.47 (2H, *d*), 4.80 (1H, *m*), 6.66 (1H, *s*), 7.49 (2H, *d*), 7.61 (2H, *d*), 7.88 (1H, *m*), and 8.23 (1H, *s*).

5



Example 419 N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}benzyl)-4-methyl-1,3-thiazol-2-amine

- 10 N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}benzyl)-4-methyl-1,3-thiazol-2-amine was prepared using the same procedure and scale as detailed for the 5-methyl analog (see above) (11 mg, 8%); RP-HPLC 8.177 min, 97 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm;
- 15 Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (DMSO- d_6 , 400 MHz) δ 1.57 (2H, *br t*), 1.67 (2H, *m*), 2.07 (2H, *m*), 2.10-2.50 (9H, *m*), 2.19 (3H, *s*), 2.54 (3H, *s*), 3.29 (2H, *m*), 4.50 (2H, *br s*), 4.79 (1H, *m*), 6.17 (1H, *s*), 7.50 (2H, *d*), 7.62 (2H, *d*), 7.99 (1H, *m*), and 8.23 (1H, *s*).

- 20 Example 420 *Cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dichloro-1,3-benzoxazol-2-amine

a) 2-Amino-6-chlorophenol

- A solution of 2-chloro-6-nitrophenol (1.210 g, 6.972 mmol) in ethanol (50 mL) was
- 25 treated with iron powder (1.947 g, 34.86 mmol) and concentrated HCl (3 mL). The

yellow mixture was heated to reflux for 18 h and then cooled to room temperature. The reaction mixture was filtered through a pad of Celite, and the filtrate was neutralized with satd aq NaHCO₃ solution. The resulting gray suspension was filtered through a pad of Celite, and the filtrate was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a black solid. Trituration with heptane afforded 2-amino-6-chlorophenol (0.577 g, 58 %) as a dark brown solid. RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 100 Å, 5 µm, 250 x 4.6 mm column) tr=7.30 min., 91%; *m/z* 143 (*MH*⁺).

b) *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dichloro-1,3-benzoxazol-2-amine was prepared from *cis*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.245 mmol) and 2-amino-4,6-dichlorophenol (0.044 g, 0.245 mmol) in a manner similar to that used in the synthesis of *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine (PH4042235). The compound was formed as an off-white solid (0.008 g, 6%): RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 100 Å, 5 µm, 250 x 4.6 mm column) tr=8.93 min., 95%; *m/z* 594 (*MH*⁺).

Example 421 *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-methyl-1,3-benzoxazol-2-amine

a) 2-Amino-4,6-dichlorophenol

2-Amino-4,6-dichlorophenol was prepared from 2,4-dichloro-6-nitrophenol (0.625 g, 2.40 mmol) in a manner similar to that described for 2-amino-6-chlorophenol. The compound was formed as a black solid (0.044g, 10%). RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 100 Å, 5 µm, 250 x 4.6 mm column) tr=9.033 min., 74%; *m/z* 177 (*MH*⁺).

b) *Cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-

d]pyrimidin-3-yl}phenyl)-7-methyl-1,3-benzoxazol-2-amine was prepared from *cis*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.245 mmol) and 2-amino-6-methylphenol (0.030 g, 0.245 mmol) in a manner similar to that used in the synthesis of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine (PH4052419F). The compound was formed as an off-white solid (0.018 g, 14%): RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 100 Å, 5 µm, 250 x 4.6 mm column) tr=7.37 min., 85%; *m/z* 539 (*MH*⁺).

10

Example 422 *Cis*- *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-chloro-1,3-benzoxazol-2-amine

a) 2-Amino-6-methylphenol

15 2-Amino-6-methylphenol was prepared from 2-methyl-6-nitrophenol (0.500 g, 3.26 mmol) in a manner similar to that described for 2-amino-6-chlorophenol. The compound was formed as a black solid (0.030g, 8%). RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 100 Å, 5 µm, 250 x 4.6 mm column) tr=5.78 min., 86%; *m/z* 123 (*MH*⁺).

20

b) *Cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-chloro-1,3-benzoxazol-2-amine was prepared from *cis*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.245 mmol) and 2-amino-6-chlorophenol (0.053 g, 0.367 mmol) in a manner similar to that used in the synthesis of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-methyl-1,3-benzoxazol-2-amine (PH4052419F). The compound was formed as an off-white solid (0.018 g, 13%): RP-HPLC (25 to 100 % CH₃CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 100 Å, 5 µm, 250 x 4.6 mm column) tr=7.78 min., 94%; *m/z* 558 (*MH*⁺).

30

Example 423 2-{4-Amino-3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1*H*-

pyrazolo[3,4-*d*]pyrimidin-1-yl}-3-pyridyl cyanide

The procedure for Suzuki coupling, used in the preparation of ethyl 2-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate, was used to couple *N*-(1,3-benzoxazol-2-yl)-
5 *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.052 g, 0.155 mmol) with 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-3-pyridyl cyanide (0.045 g, 0.124 mmol). Purification by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 10.1-11.2 min) afforded 2-{4-amino-3-
10 [4-(1,3-benzoxazol-2-ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}-3-pyridyl cyanide as a yellow powder (0.004 g, 0.009 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) *R*_t 8.55 min; MS (MH)⁺ 446.

15 Example 424 *N*1-[2-(Dimethylamino)ethyl]-2-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanamide

Ethyl 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanoate (2.03 g, 5.62 mmol), an intermediate described in the preparation of ethyl 2-[4-amino-3-
20 (4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]propanoate, was converted to the corresponding methyl ester (1.90 g, 5.47 mmol) using the esterification procedure described in the preparation of methyl 4-[4-amino-3-(4-{[(2,3-dichlorophenyl)sulfonyl]amino}-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]butanoate: RP-HPLC (25 to 100 % acetonitrile in 0.1
25 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) *R*_t 6.88 min

A portion of this methyl ester (0.110 g, 0.32 mmol) was then converted to the secondary amide with *N,N*-dimethylethylenediamine using the procedure for amide formation used to prepare *N*1-{4-[4-amino-1-(2-morpholino-2-oxoethyl)-1*H*-
30 pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-fluorophenyl}-2,3-dichloro-1-benzenesulfonamide: RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6

mm column) R_t 3.47 min

The secondary amide (0.12 g, 0.30 mmol) was coupled with *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.100 g, 0.275 mmol) using the procedure for Suzuki coupling
5 used in the preparation of ethyl 2-[4-amino-3-(4-[(2,3-dichlorophenyl)sulfonyl]amino)-3-fluorophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]acetate. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 6.3-8.3 min) afforded *N*1-[2-(dimethylamino)ethyl]-2-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanamide as a yellow
10 powder (0.0015 g, 0.003 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 7.60 min; MS (MH)⁺ 514.

15

Example 425 *N*-(4-{4-Amino-1-[2-cyano-4-(4-methylpiperazino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-*N'*-(3-methylphenyl)urea

The same procedure used to prepare *N*1-(4-{4-Amino-1-[2-cyano-4-(4-methylpiperazino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide was employed, except that the final step employed the procedure for urea formation used to prepare ethyl 2-(4-amino-3-{3-fluoro-4-[(3-toluidinocarbonyl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)acetate,
20 entailing the reaction of 2-[4-amino-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-5-(4-methylpiperazino)benzonitrile (0.018 g, 0.041 mmol) with *m*-tolyl isocyanate (0.005 mL, 0.040 mmol). Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 9.3-10.3 min) afforded *N*-(4-{4-amino-1-[2-cyano-4-(4-methylpiperazino)phenyl]-1*H*-
25 pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-*N'*-(3-methylphenyl)urea as a yellow powder (0.008 g, 0.014 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18,
30

250 x 4.6 mm column) R_t 8.03 min; MS (MH)⁺ 577.

Example 426 *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-
pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-chloro-1,3-benzothiazol-2-
amine

5 Solid 4-Bromoaniline (1.00 g, 5.81 mmol) and 2,6-dichlorobenzothiazole (1.18 g, 5.81 mmol) were heated at 140 °C for 3 days in a flask equipped with an air condenser (fusion occurred within a few minutes to give a clear liquid which solidified over the course of 3 days). The reaction mixture was allowed to cooled to
10 ambient temperature to give *N*-(4-bromophenyl)-*N*-(6-chloro-1,3-benzothiazol-2-yl)amine (1.97 g, 5.81 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 14.65 min.

Procedure for boronate formation: Crude *N*-(4-bromophenyl)-*N*-(6-chloro-
15 1,3-benzothiazol-2-yl)amine (0.178 g, 0.525 mmol), bis(pinacolato)diboron (0.180 g, 0.709 mmol), potassium acetate (0.154 g, 1.57 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (0.043 g, 0.053 mmol. [1:1 complex with dichloromethane]) in *N,N*-dimethylformamide (3 mL) in a resealable Schlenk flask were heated at 90 °C for 24 hr. The mixture was cooled to ambient
20 temperature, filtered through Celite and the crude product purified by flash column chromatography on silica gel using ethyl acetate/heptane (1:3) to afford the boronate intermediate *N*-(6-chloro-1,3-benzothiazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine as a white powder (0.116 g, 0.30 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1
25 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 15.15 min.

Procedure for Suzuki coupling: A mixture of *N*-(6-chloro-1,3-benzothiazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.116 g, 0.30 mmol), *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.106 g, 0.24 mmol) and
30 tetrakis(triphenylphosphine)palladium (0) (0.014 g, 0.012 mmol) in ethylene glycol dimethyl ether (3.0 mL), sodium carbonate (0.064 g, 0.60 mmol), and water (1.5 mL) in a sealed Schlenk flask were heated at 90 °C for 24 h. The mixture was

cooled, diluted with water (10 mL) and extracted with methanol/dichloromethane (1:19, 3 x 20 mL). The combined organic fractions were dried (magnesium sulfate), filtered, concentrated and purified by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 7.8-10.0 min) to afford *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-chloro-1,3-benzothiazol-2-amine as a yellow powder (0.036 g, 0.062 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 8.42 min; MS (MH)⁺ 574.

Example 427 *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-methoxy-1,3-benzothiazol-2-amine

Using a procedure similar to that used to prepare *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-chloro-1,3-benzothiazol-2-amine, except using 2-chloro-6-methoxybenzothiazole (0.352 g, 2.05 mmol), purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 6.3-8.3 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-methoxy-1,3-benzothiazol-2-amine as a white powder (0.046 g, 0.080 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 7.40 min; MS (MH)⁺ 570.

Example 428 *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine

A solution of fluorenylmethyloxycarbonyl isothiocyanate (1.36 g, 4.84 mmol, Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196-200) in dichloromethane (40 mL) was added via a pipet to a solution of 4-Bromoaniline (0.86 g, 5.00 mmol) in dichloromethane (10 mL) maintained at 0 °C. and the

-413-

resulting mixture stirred at ambient temperature for 14 h. The reaction was diluted with dichloromethane (60 mL) and washed with aqueous hydrochloric acid (0.5 M, 2 x 10 mL). The organic layer was dried (magnesium sulfate), filtered, and concentrated to afford the 9*H*-9-fluorenyl-methyl-*N*-[(4-

5 bromoanilino)carbothioyl]carbamate (2.25 g, 4.97 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 14.25 min.

Procedure for thiazole synthesis: 9*H*-9-fluorenyl-methyl-*N*-[(4-bromoanilino)carbothioyl]carbamate (0.25 g, 0.55 mmol) was dissolved in
10 piperidine/*N,N*-dimethylformamide (1:6, 3.5 mL) and the mixture stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure and the residue dissolved in a mixture of acetic acid (1 mL), ethanol (2 mL), and dioxane (2 mL). 1-Bromo-2-butanone (90%, 0.11 mL, 1.10 mmol) was added and the mixture was stirred for 14 h at ambient temperature. The reaction mixture was diluted with
15 half saturated aqueous sodium carbonate (15 mL) and extracted with methanol/dichloromethane (1:19, 3 x 20 mL). The combined organic layers were dried (magnesium sulfate), filtered, concentrated and purified by flash column chromatography on silica gel using ethyl acetate/heptane (1:4) to afford the bromothiazole *N*-(4-bromophenyl)-*N*-(4-ethyl-1,3-thiazol-2-yl)amine (0.15 g, 0.53
20 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 13.15 min.

The above bromothiazole intermediate was converted into the boronate using the procedure described for the preparation of *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-chloro-
25 1,3-benzothiazol-2-amine to afford the boronate intermediate *N*-(4-ethyl-1,3-thiazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.158 g, 0.48 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t
30 13.60 min.

The boronate intermediate (0.15 g, 0.45 mmol) was coupled with *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.182

g, 0.41 mmol) using the procedure for Suzuki coupling described in the preparation of *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-chloro-1,3-benzothiazol-2-amine. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 7.0-8.0 min) afforded *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine as an off-white powder (0.069 g, 0.133 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) *R*_t 7.05 min; MS (MH)⁺ 518.

Example 429 *cis*-*N*2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4,5-dimethyl-1,3-thiazol-2-amine

The procedure for thiazole synthesis, described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine, was employed with the exception that 3-bromo-2-butanone (0.183 g, 1.21 mmol) was used as the alkylating agent, and the alkylation reaction was conducted at 40 °C for 24 h. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, *R*_t 6.7-7.7 min) afforded *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4,5-dimethyl-1,3-thiazol-2-amine as an off-white powder (0.069 g, 0.133 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) *R*_t 6.83 min; MS (MH)⁺ 518.

Example 430 *cis*-*N*2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-phenyl-1,3-thiazol-2-amine

The procedure for thiazole synthesis, described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine, was employed with the exception that 2-

bromoacetophenone (0.131 g, 0.66 mmol) was used as the alkylating agent.

Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.7-9.8 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-phenyl-1,3-thiazol-2-amine as a yellow powder (0.036 g, 0.064 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 8.22 min; MS (MH)⁺ 566.

- 10 Example 431 *cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-(4-methylphenyl)-1,3-thiazol-2-amine

 The procedure for thiazole synthesis, described in the preparation of *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine, was employed with the exception that 2-bromo-4'-methylacetophenone (0.118 g, 0.554 mmol) was used as the alkylating agent. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 9.1-10.7 min) afforded *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-(4-methylphenyl)-1,3-thiazol-2-amine as an off-white powder (0.022 g, 0.038 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 8.88 min; MS (MH)⁺ 580.

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- Example 432 *cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-methyl-4-phenyl-1,3-thiazol-2-amine

 The procedure for thiazole synthesis, described in the preparation of *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine, was employed with the exception that 2-bromopropiophenone (0.081 mL, 0.532 mmol) was used as the alkylating agent, and

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the alkylation reaction was conducted at 50 °C for 24 h. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 µm Hypersil HS C18, 250 x 21 mm column, R_t 9.1-10.3 min) afforded *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-methyl-4-phenyl-1,3-thiazol-2-amine as a white powder (0.015 g, 0.026 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 µm Hypersil HS C18, 250 x 4.6 mm column) R_t 8.67 min; MS (MH)⁺ 580.

10 Example 433 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide tri-maleate

(3*R*)-3-phenylbutanoyl chloride

A solution of *R*-3-phenylbutyric acid (0.755 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethylformamide. The reaction mixture was shaken for 15 hours at room temperature under a nitrogen atmosphere. The reaction mixture was shaken for 15 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of (3*R*)-3-phenylbutanoyl chloride. The oil was directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide tri-maleate

A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL) at -5°C was treated with a solution of (3*R*)-3-phenylbutanoyl chloride (0.420 g, 2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at -5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature under a nitrogen atmosphere. (3*R*)-3-phenylbutanoyl chloride (0.210 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane

(125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide was purified by
5 flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide) in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50% (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.378 g (57%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-
10 methoxyphenyl)-(3*R*)-3-phenylbutanamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide (0.378 g, 0.649 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.226 g, 1.95 mmol) in ethyl acetate. The precipitate was filtered under nitrogen and dried on lyophilizer to give
15 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide tri-maleate. . ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.200 (s, 1H), 8.263 (s, 1H), 8.1747-8.1543 (d, 1H, *J* = 8.16 Hz), 7.312-7.282 (m, 4H), 7.235-7.232 (s, 1H), 7.211-7.168 (m, 2H), 6.114 (s, 6H), 5.061 (m, 1H), 3.890 (s, 3H), 3.301 (m, 4H), 2.997 (m, 2H), 2.783-2.741 (m,
20 6H), 2.541 (m, 8 H), 2.261-2.185 (m, 4H), 1.879 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) *R*_t 2.64 min
25 (100%).

Example 434 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-benzo[*b*]furan-2-carboxamide tri-maleate

30 benzo[*b*]furan-2-carbonyl chloride

A suspension of 2-benzofurancarboxylic acid (0.746 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and

one drop of dimethylformamide. The reaction mixture was shaken for 15 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of benzo[*b*]furan-2-carbonyl chloride. The oil was directly used in the following reaction.

- 5 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-benzo[*b*]furan-2-carboxamide tri-maleate

A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL) at -5°C was treated with a solution of benzo[*b*]furan-2-carbonyl chloride (0.415 g, 2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at -5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature under a nitrogen atmosphere. Benzo[*b*]furan-2-carbonyl chloride (0.207 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane (125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-benzo[*b*]furan-2-carboxamide was purified by flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide) in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50% (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.143 g (21%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-benzo[*b*]furan-2-carboxamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-benzo[*b*]furan-2-carboxamide (0.143 g, 0.246 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.086 g, 0.739) in ethyl acetate. The precipitate was filtered under nitrogen and dried on lyophilizer to give *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-benzo[*b*]furan-2-carboxamide tri-maleate. ¹H

NMR (DMSO- d_6 , 400 MHz) δ 9.518 (s, 1H), 8.282 (s, 1H), 8.2652-8.2447 (d, 1H, J = 8.2 Hz), 7.849-7.814 (m, 2H), 7.7813-7.7603 (d, 1H, J = 8.4 Hz), 7.562-7.523 (m, 1H), 7.418-7.369 (m, 2H), 7.338-7.313 (m, 1H), 6.088 (s, 5H), 5.10-5.00 (m, 1H), 4.003 (s, 3H), 3.529 (m, 4H), 3.314 (m, 2H), 2.971 (m, 2H), 2.778 (s, 3H), 2.497 (m, 3H), 2.209 (m, 4H), 1.909 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3 μ M, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, $C_{36}H_{44}N_6O_3$ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3 μ m particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.73 min (100%).

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Example 435 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide tri-maleate

(3*S*)-3-phenylbutanoyl chloride

15 A solution of *S*-3-phenylbutyric acid (0.755 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethylformamide. The reaction mixture was shaken for 15 hours at room temperature under a nitrogen atmosphere. The reaction mixture was shaken for 15 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of (3*S*)-3-phenylbutanoyl chloride. The oil was directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide tri-maleate

A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL) at -5°C was treated with a solution of (3*S*)-3-phenylbutanoyl chloride (0.420 g, 2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at -5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature under a nitrogen atmosphere. (3*S*)-3-phenylbutanoyl chloride (0.210 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The

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layers were partitioned, and the aqueous layer was extracted with dichloromethane (125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide was purified by flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide) in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50% (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.455 g (68%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide (0.455 g, 0.782 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.272 g, 2.35) in ethyl acetate. The precipitate was filtered under nitrogen and dried on lyophilizer to give *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide tri-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.199 (s, 1H), 8.261 (s, 1H), 8.1733-8.1528 (d, 1H, *J* = 8.2 Hz), 7.312-7.282 (m, 4H), 7.236-7.232 (m, 1H), 7.211-7.168 (m, 2H), 6.094 (s, 6H), 5.046 (m, 1H), 3.890 (s, 3H), 3.534 (m, 4H), 2.994 (m, 2H), 2.784-2.740 (m, 6H), 2.506-2.470 (m, 8H), 2.442-2.200 (m, 4H), 1.855 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) *R*_t 2.64 min (100%).

Example 436 tert-butyl *N*-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate

4-amino-1-[4-nitrophenyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidine
A suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.00 g, 7.66 mmol) in dimethylformamide (40 mL) was treated with cesium carbonate (3.74 g, 11.49

mmol) and *p*-fluoronitrobenzene (1.08 g, 7.66 mmol). The reaction mixture stirred at 80°C for 5 h under a nitrogen atmosphere. The reaction mixture was added to ice.

The precipitate was filtered and washed with water. The product, 4-amino-1-[4-nitrophenyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidine, was dried on the lyophilizer overnight to give 2.55 g (87%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.4952-8.4720 (m, 2H), 8.4142-8.3654 (m, 3H); LCMS (Perkin Elmer, Pecosphere C18 column, 3 μm particle size, 33 x 4.6 mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) *t*_R = 3.73 min (100%) *M*⁺ 380.6.

tert-butyl N-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate

A suspension of 4-amino-1-[4-nitrophenyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidine (0.500 g, 1.31 mmol) in dimethylformamide (8 mL) was treated with tert-butyl N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (0.915 g, 2.62 mmol), tetrakis(triphenylphosphine)palladium (0.091 g, 0.06 mmol), and a solution of sodium carbonate (0.333 g, 3.14 mmol) in water (4 mL). The reaction mixture stirred at 85°C for 26 h under a nitrogen atmosphere. Water was added to the reaction mixture. The precipitate was filtered and washed with water. The solid was triturated with diethyl ether to give 0.431 g, (63%) of tert-butyl N-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.6862-8.6634 (d, 2H, *J* = 9.12 Hz), 8.4897-8.4423 (m, 3H), 8.1117 (s, 1H), 8.0074-7.9872 (d, 1H, *J* = 8.08 Hz), 7.3743-7.3293 (m, 2H), 3.9189 (s, 3H), 1.4959 (s, 9H); LCMS (Perkin Elmer, Pecosphere C18 column, 3 μm particle size, 33 x 4.6 mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) *t*_R = 4.38 min *M*⁺ 478.1.

Example 437 4-amino-3-(4-amino-3-methoxyphenyl)-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine

A suspension of tert-butyl N-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate (0.386 g, 0.808 mmol) in dichloromethane (8 mL) at 0°C was treated with trifluoroacetic acid (1.6 mL). The reaction mixture stirred for 20 min at 0°C, then ice bath was removed to stir at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 18 h.

Solvent was removed under reduced pressure. Dichloromethane (15 mL) and sodium hydroxide 1N solution were added to the oil residue. The precipitate formed was filtered and dried over night on the lyophilizer to give 0.286 g (94%) of 4-amino-3-(4-amino-3-methoxyphenyl)-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.7826-8.759 (m, 2H), 8.4892-8.4296 (m, 3H), 7.1861-7.1338 (m, 2H), 6.8320-6.8121 (d, 1H, *J* = 7.96 Hz), 5.2225 (s, 2H), 3.8672 (s, 3H); LCMS (Perkin Elmer, Pecosphere C18 column, 3μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) *t*_R = 3.48 min *M*⁺ 377.6.

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Example 438 N1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-maleate

1-methyl-1*H*-2-indolecarbonyl chloride

15 A suspension of 1-methylindole-2-carboxylic acid (0.805 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethylformamide. The reaction mixture was shaken for 18 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of 1-methyl-1*H*-2-indolecarbonyl chloride. The oil was
20 directly used in the following reaction.

N1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide di-maleate

A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL)
25 at -5°C was treated with a solution of 1-methyl-1*H*-2-indolecarbonyl chloride (0.445 g, 2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at -5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature under a nitrogen atmosphere. 1-methyl-1*H*-2-indolecarbonyl chloride (0.221 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h.
30 Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The layers were partitioned, and the aqueous layer was extracted

with dichloromethane (125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide was purified by flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide) in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50% (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.463 g (68%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide (0.463 g, 0.781 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.272, 2.34 mmol) in ethyl acetate. The precipitate was filtered under nitrogen, and dried on the lyophilizer to give *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide di-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.4495 (s, 1H), 8.2848 (s, 1H), 8.1505-8.1301 (d, 1H, *J* = 8.16 Hz), 7.7232-7.7034 (d, 1H, *J* = 7.92 Hz), 7.6054-7.5844 (d, 1H, *J* = 8.4 Hz), 7.3583-7.3012 (m, 4H), 7.1778-7.1406 (m, 1H), 6.0804 (s, 4H), 5.10-5.00 (m, 1H), 4.0403 (s, 3H), 3.9614 (s, 3H), 3.5336 (m, 4H), 3.1879 (m, 2H), 2.9937 (m, 2H), 2.7836 (s, 3H), 2.4979 (m, 3H), 2.2157 (m, 4H), 1.8513 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.76 min (100%).

Example 439 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide di-maleate
1*H*-2-indolecarbonyl chloride

A suspension of indole-2-carboxylic acid (0.742 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethyl formamide. The reaction mixture was shaken for 18 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of 1*H*-2-indolecarbonyl chloride. The oil was directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide di-maleate

A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL) at -5°C was treated with a solution of 1*H*-2-indolecarbonyl chloride (0.413 g, 2.3 mmol) in dichloromethane (1 mL). The reaction mixture stirred for 20 min at -5°C. The dry ice/ acetone bath was removed and the reaction mixture stirred for 18 h under nitrogen atmosphere. 1*H*-2-indolecarbonyl chloride (0.207 g, 1.15 mmol) was added and was stirred for an additional 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred for 30 min. Organic solvent was removed under reduced pressure, and dichloromethane (25 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and reduced under pressure to give crude *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide was purified by flash chromatography on silica gel using 15 % (methanol with 2% ammonium hydroxide) in dichloromethane to still give a crude product. A second column using a gradient of 10% (methanol with 2% ammonium hydroxide) to 50% (methanol with 2% ammonium hydroxide) gave 0.139 g (21%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide (0.139 g, 0.24 mmol) in warmed ethyl acetate was treated with a warmed solution of maleic acid (0.083 g, 0.719 mmol) in ethyl acetate. The precipitate formed was

filtered under nitrogen to give 0.166 g of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide di-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.83 (s, 1H), 9.442 (s, 1H), 8.283 (s, 1H), 8.154-8.134 (d, 1H, *J* = 8.12 Hz), 7.694-7.674 (d, 1H, *J* = 8.04 Hz), 7.498-7.477 (d, 1H, *J* = 8.20 Hz), 7.407-7.402 (m, 1H), 7.352-7.325 (m, 2H), 7.267-7.229 (m, 1H), 7.112-7.074 (m, 1H), 6.078 (s, 4H), 5.10-5.00 (m, 1H), 3.974 (s, 3H), 3.525 (m, 4H), 3.178 (m, 2H), 2.975 (m, 2H), 2.771 (s, 3H), 2.457 (s, 3H), 2.208 (m, 4H), 1.909 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3 μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3 μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.67 min (100%).

Example 440 3-Phenyl-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

15 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3.0 g, 11.5 mmol) in dimethylformamide (50 mL) was treated with cesium carbonate (5.62 g, 17.25 mmol) and triphenylmethyl chloride (3.85 g, 13.8 mmol). The reaction mixture was stirred at 70°C for 22.5 h under a nitrogen atmosphere. Cesium carbonate (3.75 g, 11.5 mmol) and triphenylmethyl chloride (3.2 g, 11.5 mmol) were added to the reaction mixture and was stirred for 6.5 h. The reaction mixture was added to ice water. The precipitate was filtered and washed with water. The product, 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was dried over night on the lyophilizer. The resulting solid was triturated with ethyl acetate to give 3.05 g (53%) of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.3190-7.1106 (m, 16H); TLC (Baker Pre-coated Hard Layer Silica Gel TLC plates, Si250F₂₅₄, 30% Ethyl acetate in heptane) R_f = 0.33.

3-Phenyl-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A solution of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.0 g, 1.99 mmol) in dimethylformamide (20 mL) was treated with phenylboronic acid (0.485 g, 3.8 mmol), tetrakis(triphenylphosphine)palladium (0.138 g, 0.119 mmol), and a solution of sodium carbonate (0.506g, 4.78 mmol) in water (10 mL). The reaction

mixture was stirred at 80°C for 18.5 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and water (15 mL) was added. The precipitate was filtered and was washed with water. The crude solid was triturated with diethyl ether (30 mL). The resulting solid was dried over night on the lyophilizer to give 0.407 g (45%) of 3-phenyl-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.9416 (s, 1H), 7.6190-7.6011 (m, 2H), 7.5369-7.4493 (m, 3H), 7.3995-7.2248 (m, 15H); HPLC Waters 2690 Alliance HPLC (Symmetry Shield RP₁₈ 3.5 μm, 2.1 x 50 mm; 5%-95% acetonitrile-0.1 M ammonium acetate over 15 min, 0.5 mL/min) R_t = 11.813 min (97%).

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Example 441 *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(3*R*)-3-phenylbutanamide

(3*R*)-3-Phenylbutanoyl chloride (2.22 g, 12.18 mmol) in dichloromethane (10 mL) was added to a solution of 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclohexanone (2.86 g, 8.12 mmol) in pyridine (50 mL) at -10°C. After 15 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature overnight. Sodium hydroxide (1.0N, 15 mL) was added and the organic solvent was evaporated. The aqueous residue was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (95:5) as mobile phase to give *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(3*R*)-3-phenylbutanamide (3.11 g, 77%). ¹H NMR (CDCl₃) δ 1.40 (d, J=6.97 Hz, 3H), 2.04 (m, 1 H), 2.59-2.78 (m, 9H), 3.40 (m, 1H), 3.98 (s, 3H), 5.28 (m, 1H), 5.70 (bs, 2H), 7.15-7.35(m, 7H), 7.66 (s, 1H), 8.38 (s, 1H), 8.51 (d, J=8.18, 1H). HPLC (Waters Alliance- Column: Waters SymmetryShield, RP₁₈, 3.5 μm, 2.1x50 mm. Eluents: 5% B/A to 95% B/A in 9.0 min.(B: acetonitrile, A: 100 mM ammonia acetate buffer, pH 4.5) , 0.5 mL/min.): R_t=6.273 min.

Example 442 {4-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]phenyl}methanol

a) 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-

yl]benzaldehyde

3-(4-Phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.0 g, 6.59 mmol) was mixed with 4-fluorobenzaldehyde (1.06 mL, 9.89 mmol), cesium carbonate (4.30 g, 13.19 mmol) in DMF (6 mL). The reaction mixture was heated at 86°C

5 overnight. After cooling to room temperature, the reaction mixture was poured onto ice water. The solid was collected by filtration to give 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (2.46g, 92%). ¹H NMR (CDCl₃) δ 7.19 (m, 5H), 7.46 (m, 2H), 7.78 (d, J=8.64 Hz, 2H), 8.10 (d, J=8.70 Hz, 2H), 8.44 (s, 1H), 8.59 (d, J=8.70Hz, 2H), 10.03 (s, 1H).

10 b) {4-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]phenyl}methanol

Sodium borohydride (19 mg, 0.491 mmol) was added to a solution of 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (100 mg, 0.245 mmol) in methanol (2 mL). After 16 hours, THF (1 mL) and more
15 sodium borohydride (19 mg, 0.491mmol) was added. 5 hours later, the solvent was removed and water was added. The aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using ethyl acetate/dichloromethane (80:20 to 100:0) as mobile
20 phase to give {4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]phenyl}methanol (36 mg, 36 %). ¹H NMR (DMSO-*d*₆) δ 4.56 (s, 2H), 5.27 (bs, 1H), 7.16 (m, 5H), 7.47 (m, 4H), 7.76 (d, J=8.64 Hz, 2H), 8.18 (d, J=8.52, 2H), 8.37 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH⁺=410.1, R_t=2.43 min.

Example 443 1-{4-[(4-Methylpiperazino)methyl]phenyl}-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

30 Sodium triacetoxyborohydride (67 mg, 0.319 mmol) was added to a mixture of 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (100 mg, 0.245 mmol), 4-methylpiperazine (37 mg, 0.369 mmol),

glacial acetic acid (35 mg, 0.589 mmol) in dichloroethane (4 mL). After stirring at room temperature over night, more sodium triacetoxymethylborohydride (67 mg, 0.319 mmol) was added and the reaction mixture was stirred over night. Water (2 mL) was added and followed by sodium bicarbonate (250 mg). After stirring vigorously for 1 hour, the layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (97:3 to 80:20) as mobile phase to give 1-{4-[(4-methylpiperazino)methyl]phenyl}-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (25 mg, 21%). ^1H NMR ($\text{DMSO}-d_6$) δ 2.30 (s, 3H), 2.48(bm, 8H), 3.56 (s, 3H), 5.75 (bs, 2H), 7.11 (d, $J=8.50$, 2H), 7.18 (m, 3H), 7.40 (m, 2H), 7.48 (d, $J=8.50$ Hz, 2H), 7.29 (d, $J=8.63$ Hz, 2H), 8.12 (d, $J=8.50$ Hz, 2H), 8.47 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3 μm , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): $\text{MH}^+=492.2$, $R_t=2.97$ min.

Example 444 *tert*-Butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)carbamate

a) 1-Bromo-2-fluoro-5-methoxy-4-nitrobenzene

Potassium *tert*-butoxide (1.0 N in THF, 38 mL, 38 mmol) was added to methanol (1.54 mL, 38.0 mmol) in THF (30 mL) at 0°C . After 30 minutes, the cloudy solution was cannulated to a solution of 1-bromo-2, 5-difluoro-4-nitrobenzene (9.04g, 38.0 mmol) in THF (27 mL) at -78°C . After 30 minutes, the cooling bath was removed and the reaction mixture was allowed to warm up to 0°C . Water (250 mL) was added and 10 minutes later, the organic solvent was removed. The solid was collected by filtration to give 1-bromo-2-fluoro-5-methoxy-4-nitrobenzene (9.28 g, 98%). ^1H NMR (CDCl_3) δ 3.97 (s, 3H), 7.30 (d, $J=5.48$ Hz, 2H), 7.71 (d, $J=7.58$ Hz, 2H).

b) 4-Bromo-5-fluoro-2-methoxyaniline

Sodium hydrosulfite (14.7 g, 84.4 mmol) was added to a solution of 1-bromo-2-fluoro-5-methoxy-4-nitrobenzene (9.28 g, 37.12 mmol) in ethanol (180 mL) and

water (130 mL) at 80°C in three portions. After 5 hours the organic solvent was removed and the solid in aqueous layer was collected by filtration. The solid was further washed with heptane/ethyl acetate (3:2, 400 mL). The filtrate was evaporated to give 4-bromo-5-fluoro-2-methoxyaniline (3.29 g, 40%). ¹H NMR (DMSO-*d*₆) δ 3.75 (s, 3H), 5.22 (s, 2H), 6.56 (d, J=10.68 Hz, 2H), 6.94 (d, J=6.57 Hz, 2H).

c) *tert*-Butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate

di-*tert*-Butyl dicarbonate (3.42 g, 15.70 mmol) was mixed with 4-bromo-5-fluoro-2-methoxyaniline (3.29 g, 14.95 mmol) in THF (30 mL). The reaction mixture was heated at 65°C for 3 days with addition of di-*tert*-butyl dicarbonate (3.42 g, 15.70 mmol) every day. After removing solvent, the residue was purified by flash column chromatography using heptane/ethyl acetate (95:5 to 85:15) as mobile phase to give a mixture of the desired product *tert*-butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate and di-*tert*-butyl dicarbonate (10.4 g). Sodium hydroxide (50% solution, 2.0 mL) was added to the mixture in methanol (30mL) at 0°C and the reaction mixture was stirred at room temperature overnight. After removing solvent, water was added and the aqueous layer was extracted with heptane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to give *tert*-butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate (4.24g, 89%). ¹H NMR (CDCl₃) δ 1.52 (s, 9H), 3.85 (s, 3H), 6.93 (d, J=6.10 Hz, 1H), 7.06 (s, 1H), 8.01 (d, J=10.4 Hz, 1H).

d) *tert*-Butyl *N*-[5-fluoro-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

tert-Butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate (4.24g, 13.26 mmol), diboron pinacol ester (4.04 g, 15.91 mmol), potassium acetate (3.90 g, 39.78 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane (0.32 g, 0.40 mmol) in DMF (75 mL) was heated at 85°C overnight. Diboron pinacol ester (2.02 g, 7.96 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane (0.32 g, 0.40 mmol) was added and the heating continued for another 5 hours. After removing solvent the black residue was dissolved in dichloromethane and filtered through celite. The crude mixture was purified by

flash column chromatography using heptane/ethyl acetate (95:5 to 85:15) as mobile phase to give a mixture of *tert*-butyl *N*-[5-fluoro-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate and diboron pinacol ester (1:1 ratio, 4.23g) which was used in the next reaction without further purification

- 5 e) *trans-tert*-Butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)carbamate

trans-3-Iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.60 g, 1.36 mmol), *tert*-butyl *N*-[5-fluoro-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.0 g, 2.72 mmol),
10 palladium tetrakis(triphenylphosphine)(0.094 g, 0.082mmol) and sodium carbonate (0.35 g, 3.27 mmol) were mixed with ethylene glycol dimethyl ether (14mL) and water (7 mL). The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine,
15 dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give *trans-tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)carbamate (0.264 g, 35%). ¹H NMR (DMSO-*d*₆) δ 1.49 (s, 9H), 1.97 (m, 6H), 2.16 (s, 3H), 2.33 (m,
20 5H), 2.53 (m, 4H), 3.84 (s, 3H), 4.64 (m, 1H), 7.60 (d, J=6.78 Hz, 1H), 7.83 (d, J=11.96 Hz, 1H), 8.20 (s, 1H), 8.24 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH⁺=555.3, R_t=2.00 min.

- 25 Example 445 *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of trifluoroacetic acid/dichloromethane (20:80, 7 mL) was added to a solution of *trans-tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)carbamate (250 mg, 0.451 mmol) in dichloromethane (4.0 mL) at
30 0°C. After 15 minutes, the ice-bath was removed and the reaction mixture was stirred at room temperature for 4 hours. Solvent was then evaporated and the residue

was dissolved in dichloromethane. Saturated sodium bicarbonate was added to adjust the pH to 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated give *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (179 mg, 87%). ^1H NMR (CDCl_3) δ 1.56 (m, 2H), 2.15 (m, 7H), 2.31 (s, 3H), 2.51 (m, 4H), 2.67 (m, 4H), 3.88 (s, 3H), 4.16 (bs, 2H), 4.74 (m, 1H), 5.64 (bs, 2H), 6.56 (d, $J=10.84$ Hz, 1H), 6.88 (d, $J=6.55$ Hz, 1H), 8.33 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): $\text{MH}^+=455.2$, $R_t=0.63$ min.

Example 446 *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-*trans*-2-phenyl-1-cyclopropanecarboxamide

trans-2-Phenyl-1-cyclopropanecarbonyl chloride (32 mg, 0.176 mmol) in dichloromethane (0.3 mL) was added to a solution of *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (80 mg, 0.176 mmol) in pyridine (1.5 mL) at 0°C. After 5 minutes the ice-water bath was removed and the reaction mixture was stirred at room temperature for 3 hours. More *trans*-2-phenyl-1-cyclopropanecarbonyl chloride (32 mg, 0.176 mmol) was added to ensure the reaction went to completion. Solvent was evaporated and the residue was purified by flash column chromatography to give *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-2-phenyl-1-cyclopropanecarboxamide (93 mg, 88%). ^1H NMR ($\text{DMSO}-d_6$) δ 1.35 (m, 1H), 1.50 (m, 3H), 1.98 (m, 6H), 2.19 (s, 3H), 2.37-2.68 (m, 11H), 3.87 (s, 3H), 4.64 (m, 1H), 7.09 (m, 1H), 7.21 (m, 3H), 7.31 (m, 2H), 8.21 (m, 2H), 9.82 (m, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): $\text{MH}^+=599.3$, $R_t=1.97$ min.

Example 447 *tert*-Butyl N-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-

d]pyrimidin-3-yl]-2-methoxyphenyl}carbamate

- a) 3-Iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.5 g, 1.45 mmol), formaldehyde (30% in water, 0.16 mL, 1.60 mmol) and sodium
- 5 triacetoxyborohydride (0.43 g, 2.03 mmol) was mixed in dichloroethane (5 mL). After 4 hours, saturated sodium bicarbonate was added followed by sodium hydroxide (1.0N) to bring the pH to 10. The aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to give 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-
- 10 pyrazolo[3,4-*d*]pyrimidin-4-amine (0.275 g, 53%). ¹H NMR (DMSO-*d*₆) δ 1.85 (m, 2H), 2.09 (m, 4H), 2.22 (s, 3H), 2.88 (m, 2H), 4.75 (m, 1H), 8.19 (s, 1H), 8.32 (s, 1H).
- b) *tert*-Butyl N-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate
- 15 3-Iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (270 mg, 0.754 mmol), *tert*-butyl N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (290 mg, 0.829 mmol), palladium tetrakis(triphenylphosphine) (52 mg, 0.045 mmol) and sodium carbonate (192 mg, 1.81 mmol) were mixed with ethylene glycol dimethyl ether (8 mL) and water (4 mL).
- 20 The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase to give *tert*-butyl
- 25 N-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate (250 mg, 73%). ¹H NMR (DMSO-*d*₆) δ 1.48 (s, 9H), 1.88 (m, 2H), 2.10 (m, 2H), 2.24 (m, 5H), 2.92 (m, 2H), 3.69 (s, 3H), 4.64 (m, 1H), 7.21 (m, 2H), 7.91 (d, J=8.16 Hz, 1H), 8.04 (s, 1H), 8.23 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3
- 30 μm, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH⁺=454.2, R_t=1.67 min.

Example 448 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide tri-maleate (3*R*)-3-phenylbutanoyl chloride

- 5 A solution of *R*-3-phenylbutyric acid (0.755 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethylformamide. The reaction mixture was shaken for 15 hours at room temperature under a nitrogen atmosphere. The reaction mixture was shaken for 15 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of (3*R*)-3-phenylbutanoyl chloride. The oil was directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide tri-maleate

- A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL) at -5°C was treated with a solution of (3*R*)-3-phenylbutanoyl chloride (0.420 g, 2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at -5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature under a nitrogen atmosphere. (3*R*)-3-phenylbutanoyl chloride (0.210 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane (125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide was purified by flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide) in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50% (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.378 g (57%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-

methoxyphenyl)-(3*R*)-3-phenylbutanamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide (0.378 g, 0.649 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.226 g, 1.95 mmol) in ethyl acetate. The precipitate was filtered under nitrogen and dried on lyophilizer to give *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*R*)-3-phenylbutanamide tri-maleate. . ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.200 (s, 1H), 8.263 (s, 1H), 8.1747-8.1543 (d, 1H, *J* = 8.16 Hz), 7.312-7.282 (m, 4H), 7.235-7.232 (s, 1H), 7.211-7.168 (m, 2H), 6.114 (s, 6H), 5.061 (m, 1H), 3.890 (s, 3H), 3.301 (m, 4H), 2.997 (m, 2H), 2.783-2.741 (m, 6H), 2.541 (m, 8 H), 2.261-2.185 (m, 4H), 1.879 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3um particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.64 min (100%).

Example 449 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-benzo[*b*]furan-2-carboxamide tri-maleate

benzo[*b*]furan-2-carbonyl chloride

A suspension of 2-benzofurancarboxylic acid (0.746 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethylformamide. The reaction mixture was shaken for 15 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of benzo[*b*]furan-2-carbonyl chloride. The oil was directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-benzo[*b*]furan-2-carboxamide tri-maleate

A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL) at -5°C was treated with a solution of benzo[*b*]furan-2-carbonyl chloride (0.415 g,

2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at –5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature under a nitrogen atmosphere. Benzo[*b*]furan-2-carbonyl chloride (0.207 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane (125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-benzo[*b*]furan-2-carboxamide was purified by flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide) in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50% (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.143 g (21%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-benzo[*b*]furan-2-carboxamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-benzo[*b*]furan-2-carboxamide (0.143 g, 0.246 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.086 g, 0.739) in ethyl acetate. The precipitate was filtered under nitrogen and dried on lyophilizer to give *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-benzo[*b*]furan-2-carboxamide tri-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.518 (s, 1H), 8.282 (s, 1H), 8.2652-8.2447 (d, 1H, *J* = 8.2 Hz), 7.849-7.814 (m, 2H), 7.7813-7.7603 (d, 1H, *J* = 8.4 Hz), 7.562-7.523 (m, 1H), 7.418-7.369 (m, 2H), 7.338-7.313 (m, 1H), 6.088 (s, 5H), 5.10-5.00 (m, 1H), 4.003 (s, 3H), 3.529 (m, 4H), 3.314 (m, 2H), 2.971 (m, 2H), 2.778 (s, 3H), 2.497 (m, 3H), 2.209 (m, 4H), 1.909 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3um particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.73 min (100%).

Example 450 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide tri-maleate

5 (3*S*)-3-phenylbutanoyl chloride

A solution of *S*-3-phenylbutyric acid (0.755 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethylformamide. The reaction mixture was shaken for 15 hours at room temperature under a nitrogen atmosphere. The reaction mixture was shaken for 15 h.

10 The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of (3*S*)-3-phenylbutanoyl chloride. The oil was directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide tri-maleate

15 A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL) at -5°C was treated with a solution of (3*S*)-3-phenylbutanoyl chloride (0.420 g, 2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at -5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature
20 under a nitrogen atmosphere. (3*S*)-3-phenylbutanoyl chloride (0.210 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane
25 (125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide was purified by flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide)
30 in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50% (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.455 g (68%) pure *N*1-(4-{4-amino-1-[1-(1-

methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide (0.455 g, 0.782 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.272 g, 2.35) in ethyl acetate. The precipitate was filtered under nitrogen and dried on lyophilizer to give *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(3*S*)-3-phenylbutanamide tri-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.199 (s, 1H), 8.261 (s, 1H), 8.1733-8.1528 (d, 1H, *J* = 8.2 Hz), 7.312-7.282 (m, 4H), 7.236-7.232 (m, 1H), 7.211-7.168 (m, 2H), 6.094 (s, 6H), 5.046 (m, 1H), 3.890 (s, 3H), 3.534 (m, 4H), 2.994 (m, 2H), 2.784-2.740 (m, 6H), 2.506-2.470 (m, 8H), 2.442-2.200 (m, 4H), 1.855 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3um particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.64 min (100%).

Example 451 tert-butyl N-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate

4-amino-1-[4-nitrophenyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidine
A suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.00 g, 7.66 mmol) in dimethylformamide (40 mL) was treated with cesium carbonate (3.74 g, 11.49 mmol) and *p*-fluoronitrobenzene (1.08 g, 7.66 mmol). The reaction mixture stirred at 80°C for 5 h under a nitrogen atmosphere. The reaction mixture was added to ice. The precipitate was filtered and washed with water. The product, 4-amino-1-[4-nitrophenyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidine, was dried on the lyophilizer overnight to give 2.55 g (87%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.4952-8.4720 (m, 2H), 8.4142-8.3654 (m, 3H); LCMS (Perkin Elmer, Pecosphere C18 column, 3um particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) t_R = 3.73 min (100%) M⁺ 380.6.
tert-butyl N-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-

methoxyphenyl)carbamate

A suspension of 4-amino-1-[4-nitrophenyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidine (0.500 g, 1.31 mmol) in dimethylformamide (8 mL) was treated with tert-butyl N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (0.915 g, 2.62 mmol), tetrakis(triphenylphosphine)palladium (0.091 g, 0.06 mmol), and a solution of sodium carbonate (0.333 g, 3.14 mmol) in water (4 mL). The reaction mixture stirred at 85°C for 26 h under a nitrogen atmosphere. Water was added to the reaction mixture. The precipitate was filtered and washed with water. The solid was triturated with diethyl ether to give 0.431 g, (63%) of tert-butyl N-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.6862-8.6634 (d, 2H, *J* = 9.12 Hz), 8.4897-8.4423 (m, 3H), 8.1117 (s, 1H), 8.0074-7.9872 (d, 1H, *J* = 8.08 Hz), 7.3743-7.3293 (m, 2H), 3.9189 (s, 3H), 1.4959 (s, 9H); LCMS (Perkin Elmer, Pecosphere C18 column, 3μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) *t*_R = 4.38 min *M*⁺ 478.1.

Example 452 4-amino-3-(4-amino-3-methoxyphenyl)-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine

A suspension of tert-butyl N-(4-{4-amino-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)carbamate (0.386 g, 0.808 mmol) in dichloromethane (8 mL) at 0°C was treated with trifluoroacetic acid (1.6 mL). The reaction mixture stirred for 20 min at 0°C, then ice bath was removed to stir at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 18 h. Solvent was removed under reduced pressure. Dichloromethane (15 mL) and sodium hydroxide 1N solution were added to the oil residue. The precipitate formed was filtered and dried over night on the lyophilizer to give 0.286 g (94%) of 4-amino-3-(4-amino-3-methoxyphenyl)-1-[4-nitrophenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.7826-8.759 (m, 2H), 8.4892-8.4296 (m, 3H), 7.1861-7.1338 (m, 2H), 6.8320-6.8121 (d, 1H, *J* = 7.96 Hz), 5.2225 (s, 2H), 3.8672 (s, 3H); LCMS (Perkin Elmer, Pecosphere C18 column, 3μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) *t*_R = 3.48 min *M*⁺ 377.6.

Example 453 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-maleate

1-methyl-1*H*-2-indolecarbonyl chloride

- 5 A suspension of 1-methylindole-2-carboxylic acid (0.805 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethylformamide. The reaction mixture was shaken for 18 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of 1-methyl-1*H*-2-indolecarbonyl chloride. The oil was
10 directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide di-maleate

- A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL)
15 at -5°C was treated with a solution of 1-methyl-1*H*-2-indolecarbonyl chloride (0.445 g, 2.3 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 20 min at -5°C, then the dry ice/ acetone bath was removed and was stirred at room temperature under a nitrogen atmosphere. 1-methyl-1*H*-2-indolecarbonyl chloride (0.221 g, 1.15 mmol) was added to the reaction mixture and was stirred for 2 h.
20 Sodium hydroxide (1 N) solution (10 mL) was added and was stirred over night. The organic solvent was removed under reduced pressure, and dichloromethane (20 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane (125 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and the solvent removed under reduced
25 pressure. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide was purified by flash chromatography on silica gel using 15% (methanol with 2% ammonium hydroxide) in dichloromethane (10 min), 20% (methanol with 2% ammonium hydroxide) in dichloromethane (15 min), 50%
30 (methanol with 2% ammonium hydroxide) in dichloromethane (7 min) to give 0.463 g (68%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-

indolecarboxamide. A warmed solution of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide (0.463 g, 0.781 mmol) in ethyl acetate was treated with a warmed solution of maleic acid (0.272, 2.34 mmol) in ethyl acetate. The precipitate was filtered under nitrogen, and dried on the lyophilizer to give *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1-methyl-1*H*-2-indolecarboxamide di-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.4495 (s, 1H), 8.2848 (s, 1H), 8.1505-8.1301 (d, 1H, *J* = 8.16 Hz), 7.7232-7.7034 (d, 1H, *J* = 7.92 Hz), 7.6054-7.5844 (d, 1H, *J* = 8.4 Hz), 7.3583-7.3012 (m, 4H), 7.1778-7.1406 (m, 1H), 6.0804 (s, 4H), 5.10-5.00 (m, 1H), 4.0403 (s, 3H), 3.9614 (s, 3H), 3.5336 (m, 4H), 3.1879 (m, 2H), 2.9937 (m, 2H), 2.7836 (s, 3H), 2.4979 (m, 3H), 2.2157 (m, 4H), 1.8513 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, C₃₆H₄₄N₆O₃ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3μm particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.76 min (100%).

Example 454 *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide di-maleate

1*H*-2-indolecarbonyl chloride

A suspension of indole-2-carboxylic acid (0.742 g, 4.6 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.700 g, 5.52 mmol) and one drop of dimethyl formamide. The reaction mixture was shaken for 18 h. The solvent was removed under reduced pressure and dried under high vacuum to afford a quantitative amount of 1*H*-2-indolecarbonyl chloride. The oil was directly used in the following reaction.

*N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide di-maleate

A solution of 3-(4-amino-3-methoxyphenyl)-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.15 mmol) in pyridine (8 mL)

at -5°C was treated with a solution of 1*H*-2-indolecarbonyl chloride (0.413 g, 2.3 mmol) in dichloromethane (1 mL). The reaction mixture stirred for 20 min at -5°C. The dry ice/ acetone bath was removed and the reaction mixture stirred for 18 h under nitrogen atmosphere. 1*H*-2-indolecarbonyl chloride (0.207 g, 1.15 mmol) was added and was stirred for an additional 2 h. Sodium hydroxide (1 N) solution (10 mL) was added and was stirred for 30 min. Organic solvent was removed under reduced pressure, and dichloromethane (25 mL) was added. The layers were partitioned, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and reduced under pressure to give crude *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide was purified by flash chromatography on silica gel using 15 % (methanol with 2% ammonium hydroxide) in dichloromethane to still give a crude product. A second column using a gradient of 10% (methanol with 2% ammonium hydroxide) to 50% (methanol with 2% ammonium hydroxide) gave 0.139 g (21%) pure *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide. *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide (0.139 g, 0.24 mmol) in warmed ethyl acetate was treated with a warmed solution of maleic acid (0.083 g, 0.719 mmol) in ethyl acetate. The precipitate formed was filtered under nitrogen to give 0.166 g of *N*1-(4-{4-amino-1-[1-(1-methylpiperidin-4-yl)piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl))-1*H*-2-indolecarboxamide di-maleate. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.83 (s, 1H), 9.442 (s, 1H), 8.283 (s, 1H), 8.154-8.134 (d, 1H, *J* = 8.12 Hz), 7.694-7.674 (d, 1H, *J* = 8.04 Hz), 7.498-7.477 (d, 1H, *J* = 8.20 Hz), 7.407-7.402 (m, 1H), 7.352-7.325 (m, 2H), 7.267-7.229 (m, 1H), 7.112-7.074 (m, 1H), 6.078 (s, 4H), 5.10-5.00 (m, 1H), 3.974 (s, 3H), 3.525 (m, 4H), 3.178 (m, 2H), 2.975 (m, 2H), 2.771 (s, 3H), 2.457 (s, 3H), 2.208 (m, 4H), 1.909 (m, 2H); HPLC Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5

minutes, $C_{36}H_{44}N_6O_3$ (581.2), 95%. LCMS (Perkin Elmer, Pecosphere C18 column, 3 μ m particle size, 33 x 4.6mm; 100 % 50 mM ammonium Acetate in Water to 100% Acetonitrile over 5 min, 3.0 to 3.5 ml/min) R_t 2.67 min (100%).

5 Example 455 3-Phenyl-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3.0 g, 11.5 mmol) in dimethylformamide (50 mL) was treated with cesium carbonate (5.62 g, 17.25 mmol) and triphenylmethyl chloride (3.85 g, 13.8 mmol). The reaction mixture was
10 stirred at 70°C for 22.5 h under a nitrogen atmosphere. Cesium carbonate (3.75 g, 11.5 mmol) and triphenylmethyl chloride (3.2 g, 11.5 mmol) were added to the reaction mixture and was stirred for 6.5 h. The reaction mixture was added to ice water. The precipitate was filtered and washed with water. The product, 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was dried over night on the lyophilizer.
15 The resulting solid was triturated with ethyl acetate to give 3.05 g (53%) of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. 1H NMR (DMSO- d_6 , 400 MHz) δ 7.3190-7.1106 (m, 16H); TLC (Baker Pre-coated Hard Layer Silica Gel TLC plates, Si250F₂₅₄, 30% Ethyl acetate in heptane) R_f = 0.33.

3-phenyl-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A solution of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.0 g, 1.99 mmol) in dimethylformamide (20 mL) was treated with phenylboronic acid (0.485 g, 3.8 mmol), tetrakis(triphenylphosphine)palladium (0.138 g, 0.119 mmol), and a solution of sodium carbonate (0.506g, 4.78 mmol) in water (10 mL). The reaction mixture was stirred at 80°C for 18.5 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and water (15 mL) was added. The precipitate was filtered and was washed with water. The crude solid was triturated with diethyl ether (30 mL). The resulting solid was dried over night on the lyophilizer to give 0.407 g (45%) of 3-phenyl-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.9416 (s, 1H), 7.6190-7.6011 (m, 2H), 7.5369-7.4493 (m, 3H), 7.3995-7.2248 (m, 15H); HPLC Waters 2690 Alliance HPLC (Symmetry Shield RP₁₈ 3.5 μm, 2.1 x 50 mm; 5%-95% acetonitrile-0.1 M ammonium acetate over 15 min, 0.5 mL/min) R_t = 11.813 min (97%).

Example 456 *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(3*R*)-3-phenylbutanamide

(3*R*)-3-Phenylbutanoyl chloride (2.22 g, 12.18 mmol) in dichloromethane (10 mL) was added to a solution of 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclohexanone (2.86 g, 8.12 mmol) in pyridine (50 mL) at -10°C. After 15 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature overnight. Sodium hydroxide (1.0N, 15 mL) was added and the organic solvent was evaporated. The aqueous residue was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (95:5) as mobile phase to give *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(3*R*)-3-phenylbutanamide (3.11 g, 77%). ¹H NMR (CDCl₃) δ 1.40 (d, J=6.97 Hz, 3H), 2.04 (m, 1 H), 2.59-2.78 (m, 9H), 3.40 (m, 1H), 3.98 (s, 3H), 5.28 (m, 1H), 5.70 (bs, 2H), 7.15-7.35(m, 7H), 7.66 (s, 1H), 8.38 (s, 1H), 8.51 (d, J=8.18, 1H). HPLC (Waters Alliance- Column: Waters SymmetryShield, RP₁₈, 3.5 μm, 2.1x50 mm. Eluents: 5% B/A to 95% B/A in 9.0 min.(B: acetonitrile, A: 100

mM ammonia acetate buffer, pH 4.5), 0.5 mL/min.): $R_t=6.273$ min.

Example 457 {4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]phenyl}methanol

5 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde
3-(4-Phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.0 g, 6.59 mmol)
was mixed with 4-fluorobenzaldehyde (1.06 mL, 9.89 mmol), cesium carbonate
(4.30 g, 13.19 mmol) in DMF (6 mL). The reaction mixture was heated at 86°C
overnight. After cooling to room temperature, the reaction mixture was poured onto
10 ice water. The solid was collected by filtration to give 4-[4-amino-3-(4-
phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (2.46g, 92%). ¹H
NMR (CDCl₃) δ 7.19 (m, 5H), 7.46 (m, 2H), 7.78 (d, J=8.64 Hz, 2H), 8.10 (d,
J=8.70 Hz, 2H), 8.44 (s, 1H), 8.59 (d, J=8.70Hz, 2H), 10.03 (s, 1H).

b) {4-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-
15 yl]phenyl}methanol

Sodium borohydride (19 mg, 0.491 mmol) was added to a solution of 4-[4-
amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (100
mg, 0.245 mmol) in methanol (2 mL). After 16 hours, THF (1 mL) and more
sodium borohydride (19 mg, 0.491mmol) was added. 5 hours later, the solvent was
20 removed and water was added. The aqueous layer was extracted with
dichloromethane. The combined organic layer was washed with brine, dried over
MgSO₄, filtered and evaporated. The residue was purified by flash column
chromatography using ethyl acetate/dichloromethane (80:20 to 100:0) as mobile
phase to give {4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-
25 yl]phenyl}methanol (36 mg, 36 %). ¹H NMR (DMSO-*d*₆) δ 4.56 (s, 2H), 5.27 (bs,
1H), 7.16 (m, 5H), 7.47 (m, 4H), 7.76 (d, J=8.64 Hz, 2H), 8.18 (d, J=8.52, 2H), 8.37
(s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column:
Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B:
acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH⁺=410.1,
30 $R_t=2.43$ min.

Example 458 1-{4-[(4-Methylpiperazino)methyl]phenyl}-3-(4-phenoxyphenyl)-1*H*-

pyrazolo[3,4-*d*]pyrimidin-4-amine

Sodium triacetoxyborohydride (67 mg, 0.319 mmol) was added to a mixture of 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (100 mg, 0.245 mmol), 4-methylpiperazine (37 mg, 0.369 mmol),
5 glacial acetic acid (35 mg, 0.589 mmol) in dichloroethane (4 mL). After stirring at room temperature over night, more sodium triacetoxyborohydride (67 mg, 0.319 mmol) was added and the reaction mixture was stirred over night. Water (2 mL) was added and followed by sodium bicarbonate (250 mg). After stirring vigorously for 1 hour, the layers were separated and the aqueous layer was extracted with
10 dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (97:3 to 80:20) as mobile phase to give 1-{4-[(4-methylpiperazino)methyl]phenyl}-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (25 mg, 21%). ¹H NMR (DMSO-*d*₆) δ 2.30 (s, 3H), 2.48(bm, 8H), 3.56 (s, 3H), 5.75 (bs, 2H), 7.11 (d, J=8.50, 2H), 7.18 (m, 3H), 7.40 (m, 2H), 7.48 (d, J=8.50 Hz, 2H), 7.29 (d, J=8.63 Hz, 2H), 8.12 (d, J=8.50 Hz, 2H), 8.47 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.):
15 MH⁺=492.2, R_t=2.97 min.

Example 459 *tert*-Butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)carbamate

c) 1-Bromo-2-fluoro-5-methoxy-4-nitrobenzene

Potassium *tert*-butoxide (1.0 N in THF, 38 mL, 38 mmol) was added to
25 methanol (1.54 mL, 38.0 mmol) in THF (30 mL) at 0°C. After 30 minutes, the cloudy solution was cannulated to a solution of 1-bromo-2, 5-difluoro-4-nitrobenzene (9.04g, 38.0 mmol) in THF (27 mL) at -78°C. After 30 minutes, the cooling bath was removed and the reaction mixture was allowed to warm up to 0°C. Water (250 mL) was added and 10 minutes later, the organic solvent was removed.
30 The solid was collected by filtration to give 1-bromo-2-fluoro-5-methoxy-4-nitrobenzene (9.28 g, 98%). ¹H NMR (CDCl₃) δ 3.97 (s, 3H), 7.30 (d, J=5.48 Hz, 2H), 7.71 (d, J=7.58 Hz, 2H).

d) 4-Bromo-5-fluoro-2-methoxyaniline

Sodium hydrosulfite (14.7 g, 84.4 mmol) was added to a solution of 1-bromo-2-fluoro-5-methoxy-4-nitrobenzene (9.28 g, 37.12 mmol) in ethanol (180 mL) and water (130 mL) at 80°C in three portions. After 5 hours the organic solvent was removed and the solid in aqueous layer was collected by filtration. The solid was further washed with heptane/ethyl acetate (3:2, 400 mL). The filtrate was evaporated to give 4-bromo-5-fluoro-2-methoxyaniline (3.29 g, 40%). ¹H NMR (DMSO-*d*₆) δ 3.75 (s, 3H), 5.22 (s, 2H), 6.56 (d, J=10.68 Hz, 2H), 6.94 (d, J=6.57 Hz, 2H).

c) *tert*-Butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate

di-tert-Butyl dicarbonate (3.42 g, 15.70 mmol) was mixed with 4-bromo-5-fluoro-2-methoxyaniline (3.29 g, 14.95 mmol) in THF (30 mL). The reaction mixture was heated at 65°C for 3 days with addition of *di-tert*-butyl dicarbonate (3.42 g, 15.70 mmol) every day. After removing solvent, the residue was purified by flash column chromatography using heptane/ethyl acetate (95:5 to 85:15) as mobile phase to give a mixture of the desired product *tert*-butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate and *di-tert*-butyl dicarbonate (10.4 g). Sodium hydroxide (50% solution, 2.0 mL) was added to the mixture in methanol (30 mL) at 0°C and the reaction mixture was stirred at room temperature overnight. After removing solvent, water was added and the aqueous layer was extracted with heptane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to give *tert*-butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate (4.24g, 89%). ¹H NMR (CDCl₃) δ 1.52 (s, 9H), 3.85 (s, 3H), 6.93 (d, J=6.10 Hz, 1H), 7.06 (s, 1H), 8.01 (d, J=10.4 Hz, 1H).

d) *tert*-Butyl *N*-[5-fluoro-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

tert-Butyl *N*-(4-bromo-5-fluoro-2-methoxyphenyl)carbamate (4.24g, 13.26 mmol), diboron pinacol ester (4.04 g, 15.91 mmol), potassium acetate (3.90 g, 39.78 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane (0.32 g, 0.40 mmol) in DMF (75 mL) was heated at 85°C overnight. Diboron pinacol ester (2.02 g, 7.96 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with

dichloromethane (0.32 g, 0.40 mmol) was added and the heating continued for another 5 hours. After removing solvent the black residue was dissolved in dichloromethane and filtered through celite. The crude mixture was purified by flash column chromatography using heptane/ethyl acetate (95:5 to 85:15) as mobile phase to give a mixture of *tert*-butyl *N*-[5-fluoro-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate and diboron pinacol ester (1:1 ratio, 4.23g) which was used in the next reaction without further purification.

e) *trans-tert*-Butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)carbamate

10 *trans*-3-Iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.60 g, 1.36 mmol), *tert*-butyl *N*-[5-fluoro-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.0 g, 2.72 mmol), palladium tetrakis(triphenylphosphine)(0.094 g, 0.082mmol) and sodium carbonate (0.35 g, 3.27 mmol) were mixed with ethylene glycol dimethyl ether (14mL) and water (7 mL). The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give *trans-tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)carbamate (0.264 g, 35%). ¹H NMR (DMSO-*d*₆) δ 1.49 (s, 9H), 1.97 (m, 6H), 2.16 (s, 3H), 2.33 (m, 5H), 2.53 (m, 4H), 3.84 (s, 3H), 4.64 (m, 1H), 7.60 (d, J=6.78 Hz, 1H), 7.83 (d, J=11.96 Hz, 1H), 8.20 (s, 1H), 8.24 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH⁺=555.3, R_t=2.00 min.

Example 460 *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

30 A mixture of trifluoroacetic acid/dichloromethane (20:80, 7 mL) was added to a solution of *trans-tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-

- methoxyphenyl)carbamate (250 mg, 0.451 mmol) in dichloromethane (4.0 mL) at 0°C. After 15 minutes, the ice-bath was removed and the reaction mixture was stirred at room temperature for 4 hours. Solvent was then evaporated and the residue was dissolved in dichloromethane. Saturated sodium bicarbonate was added to
- 5 adjust the pH to 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated give *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (179 mg, 87%). ¹H NMR (CDCl₃) δ 1.56 (m, 2H), 2.15 (m, 7H), 2.31 (s, 3H), 2.51 (m, 4H), 2.67 (m, 4H), 3.88 (s, 3H), 4.16 (bs, 2H), 4.74 (m, 1H), 5.64 (bs, 2H), 6.56 (d, J=10.84 Hz, 1H), 6.88 (d, J=6.55 Hz, 1H), 8.33 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH⁺=455.2, R_t=0.63min.
- 15 Example 461 *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-*trans*-2-phenyl-1-cyclopropanecarboxamide
- trans*-2-Phenyl-1-cyclopropanecarbonyl chloride (32 mg, 0.176 mmol) in dichloromethane (0.3 mL) was added to a solution of *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (80 mg, 0.176 mmol) in pyridine (1.5 mL) at 0°C. After 5
- 20 minutes the ice-water bath was removed and the reaction mixture was stirred at room temperature for 3 hours. More *trans*-2-phenyl-1-cyclopropanecarbonyl chloride (32 mg, 0.176 mmol) was added to ensure the reaction went to completion. Solvent was
- 25 evaporated and the residue was purified by flash column chromatography to give *trans*-N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-2-phenyl-1-cyclopropanecarboxamide (93 mg, 88%). ¹H NMR (DMSO-*d*₆) δ 1.35 (m, 1H), 1.50 (m, 3H), 1.98 (m, 6H), 2.19 (s, 3H), 2.37-2.68 (m, 11H), 3.87 (s, 3H), 4.64 (m, 1H), 7.09 (m, 1H), 7.21 (m, 3H), 7.31 (m, 2H), 8.21 (m, 2H), 9.82 (m, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate
- 30

buffer, pH 4.5), 0.8 mL/min.): $MH^+ = 599.3$, $R_t = 1.97$ min.

Example 462 *tert*-Butyl N-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate

b) 3-Iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

5 3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.5 g, 1.45 mmol), formaldehyde (30% in water, 0.16 mL, 1.60 mmol) and sodium triacetoxyborohydride (0.43 g, 2.03 mmol) was mixed in dichloroethane (5 mL). After 4 hours, saturated sodium bicarbonate was added followed by sodium hydroxide (1.0N) to bring the pH to 10. The aqueous layer was extracted with
10 dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.275 g, 53%). 1H NMR ($DMSO-d_6$) δ 1.85 (m, 2H), 2.09 (m, 4H), 2.22 (s, 3H), 2.88 (m, 2H), 4.75 (m, 1H), 8.19 (s, 1H), 8.32 (s, 1H).

15 b) *tert*-Butyl N-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate

3-Iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (270 mg, 0.754 mmol), *tert*-butyl N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (290 mg, 0.829 mmol), palladium
20 tetrakis(triphenylphosphine) (52 mg, 0.045 mmol) and sodium carbonate (192 mg, 1.81 mmol) were mixed with ethylene glycol dimethyl ether (8 mL) and water (4 mL). The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over $MgSO_4$,
25 filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase to give *tert*-butyl N-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate (250 mg, 73%). 1H NMR ($DMSO-d_6$) δ 1.48 (s, 9H), 1.88 (m, 2H), 2.10 (m, 2H), 2.24 (m, 5H), 2.92 (m, 2H), 3.69 (s, 3H), 4.64 (m, 1H), 7.21 (m, 2H), 7.91 (d, $J = 8.16$ Hz, 1H), 8.04 (s, 1H), 8.23 (s, 1H). LCMS
30 (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 μm , 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50

mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): $MH^+ = 454.2$, $R_t = 1.67$ min.

Example 463 *Trans*-3-{4-[(2-chlorobenzyl)amino]-3-methoxyphenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

- 5 **Protocol A** (general procedure for reductive alkylation of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amin)

1H NMR (DMSO- d_6 , 400MHz) δ 8.18 (s, 1H), 7.46 (d, 1H), 7.30 (m, 3H), 7.08 (s, 1H), 7.01 (d, 1H), 6.42 (d, 1H), 5.96 (t, 1H), 4.59 (m, 1H), 4.45 (d, 2H), 3.90 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.22 min.

MS: MH^+ 561.

- 15 Example 464 *Trans*-3-{3-methoxy-4-[(1,3-thiazol-2-ylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

Protocol A

1H NMR (DMSO- d_6 , 400MHz) δ 8.18 (s, 1H), 7.76 (d, 1H), 7.59 (d, 1H), 7.08 (s, 1H), 7.02 (d, 1H), 6.59 (d, 1H), 6.27 (t, 1H), 4.68 (d, 2H), 4.61 (m, 1H), 3.89 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.09 min.

MS: MH^+ 534.

25

Example 465 *Trans*-3-(3-methoxy-4-[(3-methyl-1*H*-4-pyrazolyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

- 30 **Protocol A**

1H NMR (DMSO- d_6 , 400MHz) δ 8.19 (s, 1H), 7.47 (s, 1H), 7.06 (m, 3H), 6.74 (d, 1H),

5.08 (t, 1H), 4.61 (m, 1H), 4.13 (d, 2H), 3.84 (s, 3H), 2.6-2.2 (br, 9H), 2.25 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.65 min.

5 MS: MH⁺ 531.

Example 466 *Trans*-3-{3-methoxy-4-[(2-thienylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

10 **Protocol A**

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.36 (d, 1H), 7.01 (m, 4H), 6.71 (d, 1H), 5.87 (t, 1H), 4.61 (m, 3H), 3.86 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

15 ammonium acetate over 20 min, 1mL/min) R_t 13.61 min.

MS: MH⁺ 533.

Example 467 *Trans*-3-(3-methoxy-4-[(5-methyl-2-thienyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

20

Protocol A

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.04 (m, 2H), 6.84 (d, 1H), 6.70 (d, 1H), 6.62 (d, 1H), 5.77 (t, 1H), 4.61 (m, 1H), 4.47 (d, 2H), 3.86 (s, 3H), 2.6-2.2 (br, 9H), 2.37 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

25 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 20 min, 1mL/min) R_t 14.66 min.

MS: MH⁺ 547.

Example 468 *Trans*-3-(4-[(5-chloro-2-thienyl)methyl]amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

30

Protocol A

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.04 (m, 2H), 6.95 (s, 1H), 6.69 (d, 1H), 5.99 (t, 1H), 4.61 (m, 1H), 4.50 (d, 2H), 3.86 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

- 5 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.04 min.
MS: MH⁺ 567.

Example 469 *Trans*-3-(3-methoxy-4-[(2-methyl-1,3-thiazol-4-yl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

a) 2-methyl-1,3-thiazole-4-carbaldehyde

- To a solution of 4-chloromethyl-2-methyl-1,3-thiazole (1.91 g, 0.0129 mol) in toluene (50 mL), *N*-methylmorpholine-*N*-oxide (4.55 g, 0.0389 mol) was added and
15 the reaction mixture was heated at 90°C for 4 hours. *N*-methylmorpholine-*N*-oxide (1.60 g, 0.0137 mol) was added and the heating was continued for another 1.5 hours. The mixture was cooled to ambient temperature, washed with water (3x50 mL) and concentrated to yield 2-methyl-1,3-thiazole-4-carbaldehyde (1.40 g, 0.011 mol) as a brown liquid.

- 20 ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.87 (s, 1H), 8.57 (s, 1H), 2.72 (s, 3H).

TLC (ethyl acetate / heptane 1:3) R_f 0.26

b) *Trans*-3-(3-methoxy-4-[(2-methyl-1,3-thiazol-4-yl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

Protocol A

- 25 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.21 (s, 1H), 7.06 (m, 2H), 6.66 (d, 1H), 5.70 (t, 1H), 4.60 (m, 1H), 4.41 (d, 2H), 3.87 (s, 3H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.71 min.

- 30 MS: MH⁺ 548.

Example 470 *Trans*-3-{4-[(1*H*-7-indolylmethyl)amino]phenyl}-1-[4-(4-

methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

Protocol C (general procedure for reductive alkylation of *trans*- 3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amin)

- 5 ¹H NMR (DMSO-*d*₆, 400MHz) δ 11.14 (s, 1H), 8.18 (s, 1H), 7.44 (d, 1H), 7.37 (m, 3H), 7.12 (d, 1H), 6.97 (t, 1H), 6.77 (d, 2H), 6.55 (t, 1H), 6.46 (m, 1H), 4.60 (m, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.68 min.
- 10 MS: MH⁺ 536.

Example 471 *Trans*-3-{4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

- 15 **Protocol C**
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.18 (s, 1H), 7.41 (m, 4H), 7.29 (t, 1H), 6.83 (d, 2H), 6.26 (t, 1H), 4.61 (m, 1H), 4.37 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.46 min.
- 20 MS: MH⁺ 549.

- Example 472 *Trans*-1-[4-(4-methylpiperazino)cyclohexyl]-3-(4-[(5-methyl-1*H*-4-pyrazolyl)methyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate
- 25

- Protocol C**
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.49 (s, 1H), 7.35 (d, 2H), 6.76 (d, 2H), 6.07 (t, 1H), 4.59 (m, 1H), 4.06 (d, 2H), 2.6-2.2 (br, 9H), 2.21 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);
- 30 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.15 min.

MS: MH⁺ 501.

Example 473 *Trans*-3-{4-[(2-aminobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

a) *tert*-butyl *N*-[2-(hydroxymethyl)phenyl]carbamate

To a solution of di-*tert*-butyl dicarbonate (23.04 g, 0.106 mol) in anhydrous dichloromethane (150 mL) at 0°C, a solution of 2-aminobenzyl alcohol (10.0 g, 0.0812 mol) was added and the resulting mixture was stirred under an atmosphere of nitrogen at ambient temperature for 18 hours. The organic phase was washed with saturated solution of sodium bicarbonate in water (2x250 mL), dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *tert*-butyl *N*-[2-(hydroxymethyl)phenyl]carbamate (17.2 g, 0.077 mol) as a colorless oil.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.52 (s, 1H), 7.57 (d, 1H), 7.30 (d, 1H), 7.22 (t, 1H), 7.04 (t, 1H), 5.42 (t, 1H), 4.51 (d, 2H), 1.46 (s, 9H).

TLC (ethyl acetate / heptane 1:3) R_f 0.28

b) *tert*-butyl *N*-(2-formylphenyl)carbamate

A 20% dispersion of pyridinium chlorochromate in basic alumina (50 g) was added to a solution of *tert*-butyl *N*-[2-(hydroxymethyl)phenyl]carbamate (11.0 g, 0.0493 mol) in anhydrous chloroform and the resulting suspension was stirred under an atmosphere of nitrogen at ambient temperature for 1 hour. Additional 16 g of a 20% dispersion of pyridinium chlorochromate in basic alumina was added and the stirring was continued for 45 min. At this point in time, additional 15 g of of 20% dispersion of pyridinium chlorochromate in basic alumina was added and the stirring was continued for 25 min. The resulting suspension was filtered through a silica gel pad, the filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica using ethyl acetate/ n-heptane (2:98) as mobile phase to yield *tert*-butyl *N*-(2-formylphenyl)carbamate (8.67 g, 0.0392 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.31 (s, 1H), 9.95 (s, 1H), 8.18 (d, 1H), 7.87 (d, 1H), 7.67 (t, 1H), 7.24 (t, 1H), 1.49 (s, 9H).

TLC (ethyl acetate / heptane 1:5) R_f 0.56

c) *trans-tert-butyl N-2-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}anilino)methyl]phenylcarbamate acetate*

Protocol C

5 ^1H NMR ($\text{DMSO-}d_6$, 400MHz) δ 8.69 (s, 1H), 8.18 (s, 1H), 7.33 (m, 4H), 7.18 (t, 1H), 7.12 (t, 1H), 6.68 (d, 2H), 6.51 (t, 1H), 4.58 (m, 1H), 4.30 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.47 (s, 9H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.73 min.

10 d) *trans-3-{4-[(2-aminobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine diacetate*

Trans-tert-butyl N-2-[(4-4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)anilino)methyl]phenylcarbamate acetate (0.080 g, 0.000118 mol) was dissolved in dichloromethane (4 mL) at 0°C and trifluoroacetic

15 acid (1 mL) was added dropwise. The mixture was stirred at ambient temperature under an atmosphere of nitrogen for 1.5 hours, concentrated under reduced pressure and the residue purified by preparative HPLC (Hypersil C18, 8 μm , 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans-3-{4-[(2-aminobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1H-*
20 *pyrazolo[3,4-d]pyrimidin-4-amine diacetate* (0.067 g, 0.000106 mol) as a white solid.

^1H NMR ($\text{DMSO-}d_6$, 400MHz) δ 8.18 (s, 1H), 7.35 (d, 2H), 7.09 (d, 1H), 6.95 (t, 1H), 6.73 (d, 2H), 6.66 (d, 1H), 6.53 (d, 1H), 6.36 (t, 1H), 4.97 (br, 1H), 4.58 (m, 1H), 4.13 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

25 RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.87 min.

MS: MH^+ 512.

Example 474 *Trans-N1-2-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}anilino)methyl]phenylacetamide*
30 *diacetate*

To a solution of *trans-3-{4-[(2-aminobenzyl)amino]phenyl}-1-[4-(4-*

methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.050 g, 0.000079 mol) in dichloromethane (3 mL) at 0°C, *N,N*-diisopropylethylamine (0.041 g, 0.000316 mol) and acetic anhydride (0.011 g, 0.000103 mol) were successively added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The mixture was concentrated under reduced pressure and the residue purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-*N*1-2-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)methyl]phenylacetamide diacetate (0.010 g, 0.0000148 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 9.48 (s, 1H), 8.18 (s, 1H), 7.35 (m, 4H), 7.20 (m, 1H), 7.13 (m, 1H), 6.66 (d, 2H), 6.53 (t, 1H), 4.58 (m, 1H), 4.29 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.08 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.67 min.

MS: MH⁺ 554.

Example 475 *Trans*-3-[3-chloro-4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

a) *Tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate

A solution of 4-bromo-2-chloroaniline (5.00 g, 0.0242 mol) in tetrahydrofuran (50 mL) was reacted with a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (53.2 mL, 0.0532 mol). The mixture was stirred 15 minutes at ambient temperature. Di-*tert*-butyl dicarbonate (6.34 g, 0.0290 mol) was added and the solution was stirred for 2 hours. The solvent was removed *in vacuo*, and the crude material was purified by flash column chromatography on silica using heptane/ethyl acetate (4:1). The solvent was removed *in vacuo* to give *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate as a white solid (4.214 g, 0.0137 mol).

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.75 (s, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 7.50 (dd, 5H), 1.46 (s, 9H); TLC (heptane/ethylacetate 4:1) R_f 0.54.

b) *Tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)phenyl]carbamate

A mixture of *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate (2.10 g, 0.00685 mol), diboron pinacol ester (2.09 g, 0.00822 mol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.17 g, 0.00021 mol) and potassium acetate (2.02 g, 0.02055 mol) in *N,N*-dimethylformamide (50 ml) was heated at 80°C under a nitrogen atmosphere for 6 hours. The solvent was removed under reduced pressure. The residue was triturated with heptane (70 mL) and the resulting solids were removed by filtration through a pad of celite. The heptane was removed *in vacuo* to give *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate as a grey solid (1.93 g, 0.00546 mol).

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.65 (s, 1H), 7.74 (d, 1H), 7.61 (d, 1H), 7.56 (dd, 1H), 1.47 (s, 9H), 1.29 (s, 12H).

c) *Trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate

A mixture of *trans* 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.20 g, 0.00498 mol), *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.93 g, 0.00548 mol), sodium carbonate (1.32 g, 0.01245 mol) in 1,2-dimethoxyethane (50 mL) and water (100 mL) was stirred rapidly and tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred 6 hours at 80°C, after which time additional tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred an additional 16 hours at 80°C. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate (200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography on silica using dichloromethane/methanol/ammonium hydroxide (90:10:0.5). The solvent was removed *in vacuo* to give *trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate as a white solid (1.993 g, 0.00368 mol):

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.76 (s, 2H), 8.23 (s, 1H), 7.80 (d, 1H), 7.68 (d,

1H), 7.57 (dd, 1H), 4.58-4.71 (m, 1H), 2.15 (2, 3H), 1.89-2.61 (m, 15H), 1.49 (s, 9H), 1.40-1.48 (m, 2H);

TLC (dichloromethane/methanol = 90:10) R_f 0.13,

MS: MH^+ 541.

- 5 d) *Trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

Trans tert-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate (1.993 g, 0.00368 mol)

- was added to a solution of 20% trifluoroacetic acid in dichloromethane. The mixture
10 was stirred for 2 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL) and washed with 1.0 M aqueous sodium hydroxide (2 x 25 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give *trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-
15 *d*]pyrimidin-4-amine (1.564 g, 0.00355 mol) as a white solid.

1H NMR (DMSO- d_6 , 400MHz) δ 8.20 (s, 1H), 7.45 (d, 1H), 7.31 (dd, 1H), 6.92 (d, 1H), 4.57-4.63 (m, 1H), 2.23-2.55 (m, 9H), 2.14 (s, 3H), 1.89-2.08 (m, 6H), 1.38-1.52 (m, 2H);

TLC (dichloromethane/methanol = 90:10) R_f 0.08,

- 20 MS: MH^+ 441.

e) *Trans*-3-[3-chloro-4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

Salicylaldehyde (0.033 g, 0.000274 mol) and *trans*-3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.115 g,

- 25 0.000261 mol) were combined in absolute ethanol and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue dried overnight to yield *trans*-2-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)imino]methylphenol which was used without further purification.

- 30 Trimethylsulfoxonium iodide (0.110 g, 0.0005 mol) was dissolved in anhydrous dimethylsulfoxide (2 mL) and 60% dispersion of sodium hydride in paraffine (0.02 g, 0.0005 mol) was added at once. After 10 min., the solution of *trans*-2-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-

chlorophenyl) imino]methylphenol in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water (50 mL) and extracted with dichloromethane (2x40 mL). The combined organic
5 extracts were dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[3-chloro-4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
10 (0.044g, 0.000071 mol) as a white solid.
¹H NMR (DMSO-*d*₆, 400MHz) δ 8.21 (s, 1H), 7.55 (s, 1H), 7.45 (d, 1H), 7.38 (d, 1H), 7.25 (t, 1H), 7.11 (d, 1H), 6.89 (m, 2H), 5.70 (d, 1H), 5.54 (m, 1H), 4.83 (t, 1H), 4.61 (m, 1H), 4.41 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
15 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.94 min.
MS: MH⁺ 559.

Example 476 *Trans*-3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-
20 pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate
Salicylaldehyde (0.034 g, 0.000282 mol) and *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.117 g, 0.000268 mol) were combined in absolute ethanol and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the
25 residue dried overnight to yield *trans*- 2-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)imino]methylphenol which was used without further purification.
Trimethylsulfoxonium iodide (0.145 g, 0.00068 mol) was dissolved in anhydrous dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in paraffine
30 (0.027 g, 0.00068 mol) was added at once. After 10 min., the solution of *trans*- 2-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)imino]methylphenol in anhydrous dimethylsulfoxide (2 mL) was

added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water (50 mL) and extracted with dichloromethane (2x40 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.096g, 0.000142 mol) as a white solid.

- 10 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.21 (s, 1H), 7.38 (d, 1H), 7.25 (t, 1H), 7.11 (m, 2H), 6.89 (m, 3H), 5.42 (m, 1H), 5.18 (d, 1H), 4.77 (t, 1H), 4.61 (m, 1H), 4.37 (m, 1H), 3.83 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.16 min.
- 15 MS: MH⁺ 555.

Example 477 *Trans*-3-[4-(3-methyl-5-phenyl-1*H*-1-pyrazolyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

a) 1-(4-bromophenyl)-3-methyl-5-phenyl-4,5-dihydro-1*H*-pyrazole

- 20 To a solution of 1-benzoylacetone (3.63 g, 0.0224 mol) and *N,N*-diisopropylethylamine (2.88 g, 0.0224 mol) in anhydrous methanol (160 mL), 4-bromophenylhydrazine hydrochloride was added and the resulting mixture was stirred at ambient temperature for 20 hours. The solvent was removed under reduced pressure and the resulting mixture was partitioned between a 5% solution of citric acid solution in water (200 mL) and ethyl acetate (150 mL). The organic phase was successively washed with water (2x200 mL) and brine (150 mL), dried with magnesium sulfate and concentrated. The resulting residue was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (5:95) as mobile phase to yield 1-(4-bromophenyl)-3-methyl-5-phenyl-4,5-dihydro-1*H*-pyrazole (4.05 g, 0.0129 mol) as an off-white solid.
- 25
- 30

¹H NMR (DMSO-*d*₆, 400MHz) δ 7.58 (d, 2H), 7.36 (m, 3H), 7.21 (d, 2H), 7.17 (d,

2H), 6.46 (s, 1H), 2.72 (s, 3H).

TLC (ethyl acetate / heptane 1:5) R_f 0.41

b) 3-methyl-5-phenyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole

- 5 A mixture of 1-(4-bromophenyl)-3-methyl-5-phenyl-4,5-dihydro-1*H*-pyrazole (2.17 g, 0.00693 mol), diboron pinacol ester (2.11 g, 0.00832 mol), [1.1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.170 g, 0.000207 mol) and potassium acetate (2.03 g, 0.0207 mol) in *N,N*-dimethylformamide (50 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil which was purified by flash chromatography on silica using ethyl acetate/ n-heptane (7:93) as mobile phase. The resulting fractions were concentrated, the residue was triturated in n-heptane and the precipitate collected by filtration to yield 3-methyl-5-phenyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole (1.00 g, 0.00278 mol) as a white solid.

- 15 ¹H NMR (DMSO-*d*₆, 400MHz) δ 7.65 (d, 2H), 7.36 (m, 3H), 7.21 (m, 4H), 6.46 (s, 1H), 2.79 (s, 3H), 1.29 (s, 12H).

TLC (ethyl acetate / heptane 1:5) R_f 0.27

c) *trans*-3-[4-(3-methyl-5-phenyl-1*H*-1-pyrazolyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

- A mixture of 3-methyl-5-phenyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole (0.102g, 0.000283 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.104 g, 0.000236 mol), tetrakis-(triphenylphosphine)palladium (0.016 g, 0.000014 mol) and sodium carbonate monohydrate (0.073 g, 0.00055 mol) was heated in a mixture of ethylene glycol dimethyl ether (5 mL) and water (3 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60%

acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[4-(3-methyl-5-phenyl-1H-1-pyrazolyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.094g, 0.000141 mol) as a white solid.

- 5 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.64 (d, 2H), 7.37 (m, 7H), 6.49 (s, 1H), 4.63 (m, 1H), 2.6-2.2 (br, 9H), 2.30 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.10 min.

- 10 MS: MH⁺ 548.

Example 478 *Trans*-3-[4-(5-ethoxy-1H-1-pyrazolyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

a) 1-(4-bromophenyl)-1H-5-pyrazolyl ethyl ether

- 15 Ethyl acetoacetate (3.49 g, 0.02684 mol) and 4-bromophenylhydrazine hydrochloride (6.00 g, 0.02684 mol) were refluxed in acetic acid (50 mL) for 4 hours. The precipitate was removed by filtration, the filtrate concentrated under reduced pressure and the residue purified by flash chromatography on silica using ethyl acetate/ n-heptane (7:93) as mobile phase to yield 1-(4-bromophenyl)-1H-5-pyrazolyl ethyl ether
- 20 (2.63 g, 0.00936 mol) as an off-white solid.

¹H NMR (CDCl₃-*d*₆, 400MHz) δ 7.61 (d, 2H), 7.49 (d, 2H), 7.26 (s, 1H), 5.47 (s, 1H), 4.14 (q, 2H), 2.26 (s, 3H), 1.44 (t, 3H).

TLC (ethyl acetate / heptane 1:9) R_f 0.24

- 25 b) 5-ethoxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl]-1H-pyrazole

A mixture of 1-(4-bromophenyl)-1H-5-pyrazolyl ethyl ether (2.22 g, 0.00791 mol), diboron pinacol ester (2.41 g, 0.00949 mol), [1.1'-

bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with

- 30 dichloromethane (1:1) (0.194 g, 0.000237 mol) and potassium acetate (2.32 g, 0.0237 mol) in *N,N*-dimethylformamide (60 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient

temperature and the solvent removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil which was purified by flash chromatography on silica using ethyl acetate/ n-heptane (7:93) as mobile phase. The resulting fractions were concentrated, the residue was triturated in n-heptane and the precipitate collected by filtration to yield 5-ethoxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl]-1*H*-pyrazole (0.604 g, 0.00184 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 7.72 (s, 4H), 5.72 (s, 1H), 4.18 (q, 2H), 2.16 (s, 3H), 1.37 (t, 3H), 1.29 (s, 12H).

TLC (ethyl acetate / heptane 1:9) R_f 0.18

c) *trans*-3-[4-(5-ethoxy-1*H*-1-pyrazolyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of 5-ethoxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl]-1*H*-pyrazole (0.062g, 0.00019 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.070 g, 0.000159 mol), tetrakis(triphenylphosphine)palladium (0.011 g, 0.0000095 mol) and sodium carbonate monohydrate (0.049 g, 0.000398 mol) was heated in a mixture of ethylene glycol dimethyl ether (5 mL) and water (3 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[4-(5-ethoxy-1*H*-1-pyrazolyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.037g, 0.000064 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 7.85 (d, 2H), 7.71 (d, 2H), 5.75 (s, 1H), 4.65 (m, 1H), 4.21 (q, 2H), 2.6-2.2 (br, 9H), 2.18 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H), 1.40 (t, 3H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.59 min.

MS: MH⁺ 516.

Example 479 *Trans*-1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-3-methyl-4,5-dihydro-1*H*-5-pyrazolone diacetate

- A solution of *trans*-3-[4-(5-ethoxy-1*H*-1-pyrazolyl)phenyl]-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.100 g, 0.000194 mol) in 30% hydrobromic acid in acetic acid (2.5 mL) was heated at reflux for 1.5 hours. The reaction mixture was concentrated under reduced pressure and the residue neutralized with concentrated solution of ammonium hydroxide in water. The resulting suspension was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 5-45% acetonitrile – 0.1M ammonium acetate over 20 min, 21mL/min) to yield *trans*-1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-3-methyl-4,5-dihydro-1*H*-5-pyrazolone diacetate (0.066 g, 0.00011 mol) as a white solid.
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.23 (s, 1H), 8.02 (d, 2H), 7.65 (d, 2H), 4.64 (m, 1H), 2.6-2.2 (br, 9H), 2.53 (s, 2H), 2.21 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);
- RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 9.34 min.
- MS: MH⁺ 488.

Example 480 2-(2-amino-1*H*-1-imidazolyl)-1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-1-ethanone acetate

- To a mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol) and potassium carbonate (0.039 g, 0.00028 mol) in anhydrous *N,N*-dimethylformamide (3 mL) was added chloroacetylchloride (0.0031 g, 0.00028 mol) at room temperature. The mixture was stirred for 10 min. before 2-aminoimidazole sulfate (0.18 g, 0.0014 mol) and potassium carbonate (0.19g, 0.0014 mol) was added. The mixture was stirred at room temperature for 2 days then warmed to 60 °C for 6 hours. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified

by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 2-(2-amino-1*H*-1-imidazolyl)-1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-1-ethanone acetate (0.006 g, 0.00001 mol) .

5 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.27 (s, 1H), 7.71 (d, 2H), 7.44 (m, 2H), 7.19 (m, 5H), 6.55 (s, 1H), 6.36 (s, 1H), 5.76 (m, 1H), 5.30 (s, 2H), 4.59 (m, 2H), 4.40 (m, 2H), 1.90 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 9.1 min.

10 MS: MH⁺ 482

Example 481 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-[(2-hydroxyethyl)amino]-1-propanone

a) *Tert*-butyl *N*-(3-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-oxopropyl)-*N*-(2-hydroxyethyl)carbamate

15 A mixture of 1-(3-azetanyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00014 mol), 3-[(*tert*-butoxycarbonyl)(2-hydroxyethyl)amino]propanoic acid (0.038 g, 0.000175 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.034 g, 0.000175 mol),
20 *N,N*-diisopropylethylamine (0.034 g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.019 g, 0.00014 mol) in anhydrous dichloromethane (5 mL) was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to
25 yield *tert*-butyl *N*-(3-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-oxopropyl)-*N*-(2-hydroxyethyl)carbamate (0.040 g, 0.000070 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 10.3 min.

30 MS: MH⁺ 574

b) 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-[(2-hydroxyethyl)amino]-1-propanone

2 mL of an 6 N aqueous solution of hydrochloride were added to the mixture of *tert*-butyl *N*-(3-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-oxopropyl)-*N*-(2-hydroxyethyl)carbamate (0.040 g, 0.000070 mol). in acetone (5 mL). The mixture was stirred at 45 °C for 1.5 hours. The solvent was removed under removed pressure. Water (10 mL) was added to the residue, the mixture was lyophilized. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-azetanyl}-3-[(2-hydroxyethyl)amino]-1-propanone (0.003 g , 0.00001 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.27 (s, 1H), 7.69 (d, 2H), 7.42 (m, 2H), 7.19 (m, 5H), 5.70 (m, 1H), 4.67 (m, 1H), 4.57 (m, 1H), 4.40 (m, 1H), 4.31 (m, 1H), 3.40 (m, 2H), 2.74 (m, 2H), 2.51 (m, 2H), 2.29 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 8.7 min.

MS: MH⁺ 474

Example 482 2-(2-amino-1*H*-1-imidazolyl)-1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-1-ethanone acetate

To a mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00013 mol) and potassium carbonate (0.036 g, 0.00026 mol) in anhydrous *N,N*-dimethylformamide (3 mL) was added chloroacetylchloride (0.028 g, 0.00026 mol) at room temperature. The mixture was stirred for 10 min. before 2-aminoimidazole sulfate (0.18 g, 0.0014 mol) and potassium carbonate (0.19 g, 0.0014 mol) were added. The mixture was stirred at room temperature for 18 hours then warmed to 60 °C for 6 hours. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 2-(2-amino-1*H*-1-imidazolyl)-1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-1-ethanone acetate (0.015 g, 0.00003 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.26 (s, 1H), 7.67 (d, 2H), 7.44 (m, 2H), 7.17 (m, 5H), 6.52 (s, 1H), 6.38 (s, 1H), 5.49 (br, 2H), 4.99 (m, 1H), 4.76 (m, 2H), 4.59 (m, 1H), 3.99 (m, 1H), 3.30 (m, 1H), 2.80 (m, 1H), 2.20 (m, 1H), 1.99 (m, 3H), 1.90 (s, 3H).

- 5 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 9.4 min.

MS: MH⁺ 510

- Example 483 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-[(2-hydroxyethyl)amino]-1-ethanone

- To a mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00013 mol) and potassium carbonate (0.036 g, 0.00026 mol) in anhydrous *N,N*-dimethylformamide (3 mL) was added chloroacetylchloride (0.028 g, 0.00026 mol) at room temperature. The mixture was stirred for 10 min. before ethanolamine (0.078 mL, 0.0013 mol) was added. The mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and washed with water (2 mL). The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-2-[(2-hydroxyethyl)amino]-1-ethanone (0.022 g, 0.00005 mol).

- ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.26 (s, 1H), 7.67 (d, 2H), 7.44 (m, 2H), 7.17 (m, 5H), 5.03 (br, 1H), 5.00 (br, 1H), 4.52 (m, 1H), 4.05 (m, 1H), 3.87 (m, 2H), 3.64 (m, 2H), 2.96 (m, 2H), 2.92 (m, 2H), 2.17 (m, 1H), 1.90 (m, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 9.0 min.

MS: MH⁺ 488

- Example 484 Synthesis of 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-[(2-hydroxyethyl)amino]-1-propanone *Tert*-butyl *N*-(3-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-

pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-oxopropyl)-*N*-(2-hydroxyethyl)carbamate

A mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.05 g, 0.00013 mol), 3-[(*tert*-butoxycarbonyl)(2-hydroxyethyl)amino]propanoic acid (0.038 g, 0.000163 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.031 g, 0.000163 mol), *N,N*-diisopropylethylamine (0.031 g, 0.00024 mol) and 1-hydroxy-7-azabenzotriazole (0.018 g, 0.00013 mol) in anhydrous dichloromethane (5 mL) was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield *tert*-butyl *N*-(3-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-oxopropyl)-*N*-(2-hydroxyethyl)carbamate (0.050 g, 0.000083 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) *R_t* 10.4 min.

MS: *MH*⁺ 602

b) 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-[(2-hydroxyethyl)amino]-1-propanone 2 mL of an 6 N aqueous solution of hydrochloride were added to the mixture of *tert*-butyl *N*-(3-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-oxopropyl)-*N*-(2-hydroxyethyl)carbamate (0.050 g, 0.000083 mol) in acetone (5 mL). The mixture was stirred at 45 °C for 1.5 hours. The solvent was removed under reduced pressure. Water (10 mL) was added to the residue, the mixture was lyophilized. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}-3-[(2-hydroxyethyl)amino]-1-propanone (0.014 g , 0.00003 mol) .

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.25 (s, 1H), 7.67 (d, 2H), 7.42 (m, 2H), 7.19 (m, 5H), 4.98 (m, 1H), 4.52 (m, 2H), 4.04 (m, 1H), 3.31 (m, 2H), 2.81 (m, 2H), 2.78 (m, 1H), 2.74 (m, 2H), 2.58 (m, 2H), 1.99 (m, 1H), 1.90 (m, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

ammonium acetate over 10 min, 1mL/min) R_t 9.1 min.

MS: MH⁺ 502

5 Example 485 Synthesis of 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetic acid

a) *Tert*-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetate

To a mixture of 3-(4-phenoxyphenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.10 g, 0.00026 mol, 1 eq.) and potassium carbonate (0.072 g, 0.000526 mol, 2 eq.) in anhydrous *N, N*-dimethylformamide (8 mL) was added *tert*-butyl 2-bromoacetate (0.0768 g, 0.00039 mol, 1.5 eq.) at room temperature. The mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and washed with water (3 mL). The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using methanol/
10 dichloromethane (5:95) as mobile phase to yield *tert*-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetate (0.10g, 0.0002 mol).

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M
20 ammonium acetate over 10 min, 1mL/min) R_t 11.8 min.

MS: MH⁺ 501

2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetic acid

2 mL of an 6 N aqueous solution of hydrochloride were added to the mixture
25 of *tert*-butyl 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetate (0.10 g, 0.0002 mol) in acetone (5 mL). The mixture was stirred at 45 °C for 2 hours. The solvent was removed under reduced pressure. Water (10 mL) was added into the residue, and the mixture was lyophilized to yield
30 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetic acid (0.010 g, 0.0002 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.50 (s, 1H), 7.69 (d, 2H), 7.43 (m, 2H), 7.19 (m, 5H), 5.07 (m, 1H), 4.02 (s, 2H), 3.50 (br, 2H), 3.42 (br, 2H), 2.53 (br, 2H), 2.25 (br,

2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 8.7 min.

MS: MH⁺ 445

5

Example 486 *N*1-(1*H*-2-imidazolyl)-2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetamide

A mixture of 2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetic acid (0.06 g, 0.00013 mol), 2-aminoimidazole sulfate (0.022 g, 0.000163 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.031 g, 0.000163 mol), *N,N*-diisopropylethylamine (0.047 g, 0.00036 mol) and 1-hydroxy-7-azabenzotriazole (0.018 g, 0.00013 mol) in anhydrous dichloromethane (8 mL) was stirred for 18 hours at room temperature. Additional 2-aminoimidazole sulfate (0.022 g, 0.000163 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.031 g, 0.000163 mol), *N,N*-diisopropylethylamine (0.047 g, 0.00036 mol) and 1-hydroxy-7-azabenzotriazole (0.018 g, 0.00013 mol), were added and the mixture was stirred for 18 hour at room temperature. The mixture was warmed to 50 °C for 6 hours, then stirred at room temperature for 2 days. The solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield *N*1-(1*H*-2-imidazolyl)-2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}acetamide (0.005 g, 0.00001 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.24 (s, 1H), 7.68 (d, 2H), 7.43 (m, 2H), 7.19 (m, 5H), 6.80 (br, 1H), 6.70 (br, 1H), 4.80 (br, 1H), 3.06 (s, 2H), 3.05 (m, 2H), 2.43 (m, 2H), 2.33 (m, 2H), 1.92 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 9.2 min.

MS: MH⁺ 510

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Example 487 *Trans* *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-phenyl-1-cyclopropanecarboxamide

maleate

a) Benzyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

To a mixture of 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (13.86 g, 0.0333 mol) and sodium bicarbonate (8.4 g, 0.0999 mol) in water (140 mL) was added benzylchloroformate (6.48 g, 0.0383 mol) in dioxane (120 mL) at room temperature. The mixture was stirred at room temperature under an atmosphere of nitrogen for 18 hours. The yellow solid was filtered and washed with ethyl ether to yield benzyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (12 g, 0.025 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 10.5 min.

MS: MH^+ 479

b) Benzyl 4-(4-amino-3-{4-[(*tert*-butoxycarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

A mixture of benzyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (7.0 g, 0.0146 mol), *tert*-butyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (6.15 g, 0.0176 mol), tetrakis(triphenylphosphine)palladium (1.0 g, 0.000876 mol) and sodium carbonate (3.9 g, 0.0365 mol) in ethylene glycol dimethyl ether (170 mL) and water (70 mL) was heated at 75 °C for 16 hours under an atmosphere of nitrogen. After addition of *tert*-butyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (6.15 g, 0.0176 mol, 1.2 eq.) and tetrakis(triphenylphosphine)palladium (1.0 g, 0.000876 mol) the mixture was stirred at 85 °C for additional 16 hours. The mixture was allowed to cool to ambient temperature and ethylene glycol dimethyl ether was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 20 % - 40 % ethyl acetate / dichloromethane followed by 2 % - 5 % methanol / dichloromethane as a mobile phase to give benzyl 4-(4-amino-3-{4-[(*tert*-butoxycarbonyl)amino]-3-

methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (8.0 g, 0.014 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 12.6 min.

5 MS: MH⁺ 574

c) Benzyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

To a mixture of benzyl 4-(4-amino-3-{4-[(*tert*-butoxycarbonyl)amino]-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (7.68 g, 0.0134 mol) in dichloromethane (10 mL) was added a 25 % solution of trifluoroacetic acid in dichloromethane at 0 °C. The mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours. The solvents were removed under reduced pressure. The residue was cooled to 0 °C and basified with an aqueous 5 N solution of sodium hydroxide. The aqueous layer was extracted with
15 dichloromethane (3 x 150 mL). The combined organic layer was washed with water and brine, and dried over magnesium sulfate. The solvents were removed under reduced pressure to give benzyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (6.02 g, 0.0127 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 10.3 min.

20 MS: MH⁺ 474

d) *Trans* benzyl 4-[4-amino-3-(3-methoxy-4-{[(2-phenylcyclopropyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

To a mixture of benzyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (3.0 g, 0.0063 mol) in pyridine (100 mL) was added racemic *trans*-2-phenyl-cyclopropane carbonyl chloride (1.163 g, 0.007 mol) at –5 °C. The mixture was stirred at –5 °C for 10 minutes then warmed up to room temperature and stirred for 1.5 hours. The mixture was quenched with an
30 aqueous 1N solution of sodium hydroxide. Organic solvents were removed under reduced pressure. The residue was partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was washed with a 5 % aqueous solution of

citric acid (3 x 100 mL), 1 N aqueous solution of hydrochloride (3 x 100 mL), water, saturated aqueous solution of sodium bicarbonate, and brine, and dried over magnesium sulfate. The solvents were removed under reduced pressure to give *trans* benzyl 4-[4-amino-3-(3-methoxy-4-[(2-

5 phenylcyclopropyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (3.47 g, 0.006 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) *R*_t 11.5 min.

MS: MH^+ 618

10 e) *Trans* N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide maleate
The mixture of *trans* benzyl 4-[4-amino-3-(3-methoxy-4-[(2-phenylcyclopropyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (3.4 g, 0.0055 mol) and 20 % palladium hydroxide on carbon
15 (0.4 g) in ethanol (150 mL) was stirred under atmosphere of hydrogen at room temperature for 18 hours. The mixture was filtered and solvents were removed. To the residue 20 % palladium hydroxide on carbon (0.4 g), acetic acid (0.25 mL) in ethanol (60 mL) and ethyl acetate (40 mL) were added. The mixture was stirred under atmosphere of hydrogen at room temperature for additional 18 hours. The
20 mixture was filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica using 25 % - 50 % methanol / dichloromethane to give *trans* N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide (1.36 g, 0.0028 mol). *Trans* N1-{4-[4-amino-1-(4-
25 piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide (0.05 g, 0.000104 mol) in ethyl acetate (5 mL) was heated to 40 °C. Maleic acid (0.00133 g, 0.000114 mol) was dissolved in warm ethyl acetate before added into the mixture. The mixture was stirred at 40 °C for 10 minutes then cooled to room temperature. The white precipitates were filtered to
30 give *trans* N1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide maleate (0.0044 g, 0.00001 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.65 (s, 1H), 8.26 (m, 2H), 7.25 (m, 7H), 6.01 (d, 2H), 5.09 (br, 1H), 3.90 (s, 3H), 3.48 (m, 2H), 3.18 (m, 2H), 2.61 (br, 1H), 2.37 (m, 3H), 2.13 (m, 2H), 1.50 (br, 1H), 1.34 (br, 1H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M

5 ammonium acetate over 10 min, 1mL/min) R_t 9.0 min.

MS: MH⁺ 484

Example 488 *N*1-(4-{4-amino-1-[1-(1*H*-2-imidazolylmethyl)-4-piperidyl]-1*H*-
pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)- (1*S*,2*S*)/(1*R*,2*R*)-
10 2-phenyl-1-cyclopropanecarboxamide

A mixture of *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}- (1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide (0.10 g, 0.00021 mol), 2-imidazole carboxaldehyde (0.022 g, 0.00023 mol), and acetic acid (0.037 g, 0.0006 mol) in dichloroethane (8 mL) was stirred at room temperature
15 under an atmosphere of nitrogen for 1.5 hrs. Sodium triacetoxyborohydride (0.133 g, 0.00063 mol) was added into the mixture and stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. Additional acetic acid (0.037 g, 0.0006 mol), 2-imidazole carboxaldehyde (0.011 g, 0.00012 mol), and sodium
triacetoxyborohydride (0.133 g, 0.00063 mol) were added to the mixture and the
20 mixture was stirred for 18 hours. The reaction was quenched with an aqueous 5*N* solution of sodium hydroxide. The solvents were removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The organic layer was washed with water and brine. The solvents were removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x
25 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield *N*1-(4-{4-amino-1-[1-(1*H*-2-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)- (1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide (0.019 g, 0.000034 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.8 (br, 1H), 9.63 (s, 1H), 8.22 (m, 2H), 7.25
30 (m, 7H), 6.99 (br, 1H), 6.83 (br, 1H), 4.68 (br, 1H), 3.90 (s, 3H), 3.56 (s, 2H), 2.93 (m, 2H), 2.58 (br, 1H), 2.37 (br, 1H), 2.22 (m, 3H), 1.90 (m, 3H), 1.50 (br, 1H), 1.30 (br, 1H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 9.4 min.

MS: MH^+ 564

- 5 Example 489 *N*1-[4-(4-amino-1-{1-[(1-methyl-1*H*-2-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide

A mixture of *N*1-[4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-(1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide (0.10 g,
10 0.00021 mol), 1-methyl-2-imidazole carboxaldehyde (0.025 g, 0.00023 mol), and acetic acid (0.037 g, 0.0006 mol) in dichloroethane (8 mL) was stirred at room temperature under an atmosphere of nitrogen for 1.5 hrs. Sodium triacetoxymethylborohydride (0.133 g, 0.00063 mol) was added into the mixture and stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The reaction
15 was quenched with an aqueous 5*N* solution of sodium hydroxide. The solvents were removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The organic layer was washed with water and brine. The solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel using 5 % - 50 % methanol/ dichloromethane as
20 mobile phase to yield *N*1-[4-(4-amino-1-{1-[(1-methyl-1*H*-2-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(1*S*,2*S*)/(1*R*,2*R*)-2-phenyl-1-cyclopropanecarboxamide (0.070 g, 0.00012 mol).

1H NMR (DMSO-*d*₆, 400 MHz) δ 9.63 (s, 1H), 8.22 (m, 2H), 7.25 (m, 7H), 7.09 (s, 1H), 6.75 (s, 1H), 4.68 (br, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 3.20 (s, 2H), 2.93 (m,
25 2H), 2.58 (br, 1H), 2.35 (br, 1H), 2.24 (m, 4H), 1.89 (m, 2H), 1.50 (br, 1H), 1.30 (br, 1H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 9.6 min.

MS: MH^+ 578

30

- Example 490 3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

a) Benzyl 4-[4-amino-3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

A mixture of benzyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (3.0 g, 0.0063 mol), 5-methylfurfural (0.77 g, 0.007 mol), and acetic acid (1.15 g, 0.019 mol) in dichloroethane (100 mL) was stirred at room temperature under an atmosphere of nitrogen for 1.5 hrs. Sodium triacetoxyborohydride (4.1 g, 0.0195 mol) was added to the mixture and the mixture was stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The reaction was quenched with an aqueous 5N solution of sodium hydroxide. The solvents were removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 200 mL), and the combined organic layer was washed with water and brine, and dried over magnesium sulfate. The solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel using 2 % - 5 % methanol/ dichloromethane as mobile phase to yield benzyl 4-[4-amino-3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (2.63 g, 0.0046 mol). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 11.59 min.

MS: MH⁺ 568

b) 3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of benzyl 4-[4-amino-3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.18 g, 0.000317 mol) and 20 % palladium hydroxide on carbon (0.02 g) in ethyl acetate (10 mL) was stirred under atmosphere of hydrogen at room temperature for 18 hours. The mixture was filtered and solvents were removed. The residue was purified by flash column chromatography on silica using 5 % - 10 % methanol / dichloromethane (2 % NH₄OH) to give 3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.02 g, 0.000046 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.20 (s, 1H), 7.07 (m, 2H), 6.78 (m, 1H), 6.18 (s,

1H), 5.97 (s, 1H), 5.59 (m, 1H), 4.79 (br, 1H), 4.31 (m, 2H), 3.86 (s, 3H), 3.16 (m, 2H), 2.74 (m, 2H), 2.23 (s, 3H), 2.15 (m, 2H), 1.90 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 8.7 min.

5 MS: MH⁺ 434

Example 491 3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-{1-[(1-methyl-1H-2-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine.

10 A mixture 3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.045 g, 0.0001 mol), 1-methyl-2-imidazole carboxaldehyde (0.011 g, 0.00011mol), and acetic acid (0.018 g, 0.0003 mol) in dichloroethane (4 mL) was stirred at room temperature under an atmosphere of nitrogen for 1.5 hrs. Sodium triacetoxymethylborohydride (0.064 g, 0.0003 mol) was
15 added into the mixture and the mixture was stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The reaction was quenched with an aqueous 5 N solution of sodium hydroxide. The solvents were removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The organic layer was washed with water and brine. The solvents were removed under
20 reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 3-(3-methoxy-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-{1-[(1-methyl-1H-2-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.03 g, 0.00006 mol).

25 ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.19 (s, 1H), 7.16 (s, 1H), 7.06 (m, 2H), 6.86 (s, 1H), 6.77 (d, 1H), 6.18 (s, 1H), 5.98 (s, 1H), 5.59 (m, 1H), 4.67 (br, 1H), 4.31 (m, 2H), 3.85 (s, 3H), 3.71 (s, 3H), 3.66 (s, 2H), 2.96 (m, 2H), 2.27 (m, 2H), 2.23 (s, 3H), 2.18 (m, 2H), 1.91 (m, 2H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 9.5 min.

30 MS: MH⁺ 528

Example 492 *Trans* N1-(4-{4-amino-1-[(4-hydroxy-4-piperidyl)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-phenyl-1-cyclopropanecarboxamide

5 a) *Tert*-butyl 4-[(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl]-4-hydroxy-1-piperidinecarboxylate

A mixture of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.86 g, 0.0033 mol), *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (0.7 g, 0.0033 mol) and cesium carbonate (1.1 g, 0.0033 mol) in anhydrous *N,N*-dimethylformamide (30 mL) was stirred at 60 °C for 18 hours. The solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane (200 mL). The organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was triturated with dichloromethane, and the solid was filtered to give *tert*-butyl 4-[(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl]-4-hydroxy-1-piperidinecarboxylate (0.66 g, 0.0014 mol).

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.7 min.

MS: MH⁺ 475

20 b) *Tert*-butyl 4-{[4-amino-3-(4-{[(benzyloxy)carbonyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl]-4-hydroxy-1-piperidinecarboxylate

A mixture of *tert*-butyl 4-[(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl]-4-hydroxy-1-piperidinecarboxylate (0.27 g, 0.00057 mol), benzyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (0.26 g, 0.00068 mol), tetrakis(triphenylphosphine)palladium (0.039 g, 0.000034 mol) and sodium carbonate (0.15 g, 0.0014 mol) in ethylene glycol dimethyl ether (7 mL) and water (3 mL) was heated at 85 °C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and ethylene glycol dimethyl ether was removed under the reduced pressure. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with water and brine, and dried over magnesium sulfate. The organic layer was filtered through silica gel twice to remove the catalyst, and the solvent was removed under reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8µm, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate,

21mL/min) to yield *tert*-butyl 4-{[4-amino-3-(4-{[(benzyloxy)carbonyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl}-4-hydroxy-1-piperidinecarboxylate (0.1 g, 0.00017 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

5 ammonium acetate over 10 min, 1mL/min) Rt 10.9 min.

MS: MH⁺ 604

c) *Tert*-butyl 4-{[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl}-4-hydroxy-1-piperidinecarboxylate

A mixture of *tert*-butyl 4-{[4-amino-3-(4-{[(benzyloxy)carbonyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl}-4-hydroxy-1-piperidinecarboxylate (0.1 g, 0.000017 mol) and palladium on carbon (0.01 g) in ethanol (2.5 mL) and tetrahydrofuran (2.5 mL) was stirred under atmosphere of hydrogen at room temperature for 18 hours. The mixture was filtered and additional palladium on carbon (0.01 g) was added. The mixture was stirred under atmosphere of hydrogen at room temperature for 18 hours. The mixture was filtered through celite and the solvents were removed under reduced pressure to give *tert*-butyl 4-{[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl}-4-hydroxy-1-piperidinecarboxylate (0.08 g, 0.00017 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

20 ammonium acetate over 10 min, 1mL/min) Rt 8.8 min.

MS: MH⁺ 470

d) *Trans tert*-butyl 4-{[4-amino-3-(3-methoxy-4-{[(2-phenylcyclopropyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl}-4-hydroxy-1-piperidinecarboxylate

25 To a mixture of *tert*-butyl 4-{[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl}-4-hydroxy-1-piperidinecarboxylate (0.08 g, 0.00017 mol) in pyridine (4 mL) was added *trans*-2-phenyl-cyclopropane carbonyl chloride (0.035g, 0.00019 mol) at –5 °C. The mixture was stirred at –5 °C for 10 minutes then warmed up to room temperature to stir for 1 hours. The mixture was quenched with an aqueous 1N solution of sodium hydroxide. Pyridine was removed under reduced pressure. The residue was partitioned between water and dichloromethane (50 mL). The organic layer was washed with water. The solvents

were removed under reduced and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield *trans tert*-butyl 4-[[4-amino-3-(3-methoxy-4-[(2-phenylcyclopropyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl]-4-hydroxy-1-piperidinecarboxylate (0.08 g, 0.00013 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 10.7 min.

MS: MH⁺ 614

e) *Trans N1*-(4-{4-amino-1-[(4-hydroxy-4-piperidyl)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-phenyl-1-cyclopropanecarboxamide hydrochloride salt. A mixture of *trans tert*-butyl 4-[[4-amino-3-(3-methoxy-4-[(2-phenylcyclopropyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl]-4-hydroxy-1-piperidinecarboxylate (0.08 g, 0.00013 mol) in acetone (12 mL) and 6 N aqueous hydrochloride solution (3 mL) was stirred at 40 °C for 2 hours. Acetone was removed under reduced pressure, and the residue was lyophilized to give *trans N1*-(4-{4-amino-1-[(4-hydroxy-4-piperidyl)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-phenyl-1-cyclopropanecarboxamide hydrochloride salt (0.07 g, 0.00012 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.65 (s, 1H), 8.71 (br, 1H), 8.43 (s, 1H), 8.26 (m, 1H), 7.25 (m, 7H), 4.40 (s, 2H), 3.90 (s, 3H), 3.10 (m, 2H), 2.98 (m, 2H), 2.51 (m, 1H), 2.34 (m, 1H), 1.89 (m, 2H), 1.71 (m, 2H), 1.48 (m, 1H), 1.31 (m, 1H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 8.7 min.

MS: MH⁺ 514

Example 493 *N1*-4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-(1*S*,2*S*)/(1*R*,2*R*)-2-phenylcyclopropane-1-carboxamide.

A suspension of 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclohexanone (2.00 g, 0.00568 mol) in pyridine (20 mL) was cooled to – 10° C. A solution of racemic *trans*-2-benzylcyclopropane-1-carbonyl chloride (1.53 g, 0.00852 mol) in dichloromethane (5 mL) was added dropwise,

keeping the temperature less than to -5°C . The reaction mixture was allowed to come to ambient temperature over four hours. Aqueous sodium hydroxide (1.0 M, 10 mL) was added and the mixture was stirred 1 hour. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (25 mL) and water (50 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo* to give *N*1-4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-(1*S*,2*S*)-2-phenylcyclopropane-1-carboxamide as a white solid (1.603 g, 0.00323 mol).

¹H NMR (DMSO-*d*₆, 400MHz) δ 9.64 (s, 1H), 8.27 (s, 1H), 8.23 (d, 1H), 7.14-7.35 (m, 7H), 5.24-5.27 (m, 1H), 3.90 (s, 3H), 2.65-2.78 (m, 2H), 2.56-2.63 (m, 1H), 2.34-2.37 (m, 5H), 2.20-2.30 (m, 2H), 1.45-1.53 (m, 1H), 1.28-1.35 (m, 1H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*_t 15.04 min.;

MS: *MH*⁺ 497.

Example 494 *Cis N*1-(4-{4-amino-1-[4-(ammoniomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(1*S*,2*S*)/(1*R*,2*R*)-2-phenylcyclopropane-1-carboxamide acetate.

a) *Cis N*1-4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-(1*S*,2*S*)-2-phenylcyclopropane-1-carboxamide

In a heat dried flask, trimethylsulfoxonium iodide (0.425 g, 0.00193 mol) in dimethylsulfoxide (5 ml) was reacted with 60% sodium hydride dispersion in mineral oil (0.071 g, 0.00193 mol). The mixture was stirred at room temperature for 30 minutes and then cooled to 10°C . A solution of *N*1-4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-(1*S*,2*S*)/(1*R*,2*R*)-2-phenylcyclopropane-1-carboxamide (0.800 g, 0.00161 mol) in dimethylsulfoxide (5 ml) was added, and the mixture was stirred at ambient temperature for 6 hours. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic phase was washed with water (5 mL), brine (5 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give *cis N*1-4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-(1*S*,2*S*)/(1*R*,2*R*)-2-phenylcyclopropane-1-carboxamide as a

white solid (0.820 g, 0.00160 mol):

^1H NMR (DMSO- d_6 , 400MHz) δ 9.64 (s, 1H), 8.24 (s, 1H), 8.22 (d, 1H), 7.17-7.31 (m, 7H), 4.84-4.90 (m, 1H), 3.92 (s, 3H), 2.70 (s, 2H), 2.56-2.63 (m, 1H), 2.34-2.42 (m, 1H), 2.12-2.33 (m, 4H), 1.90-1.99 (m, 2H), 1.44-1.52 (m, 1H), 1.27-1.37 (m, 3H);

5 MS: MH^+ 413.

b) *Cis* N1-(4-{4-amino-1-[4-(ammoniomethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(1*S*,2*S*)/(1*R*,2*R*)-2-phenylcyclopropane-1-carboxamide acetate.

A mixture of *cis* N1-4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-(1*S*,2*S*)/(1*R*,2*R*)-2-phenylcyclopropane-1-carboxamide (0.200 g, 0.000391 mol) in 2-propanol (5 mL) and ammonium hydroxide (5 mL) was heated at 65° C in a pressure tube for 18 hours. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8 μm , 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *cis* N1-(4-{4-amino-1-[4-(ammoniomethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(1*S*,2*S*)/(1*R*,2*R*)-2-phenylcyclopropane-1-carboxamide acetate as a white solid (0.112 g, 0.000212 mol):

20 ^1H NMR (DMSO- d_6 , 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.59-4.80 (m, 1H), 3.91 (s, 3H), 2.28-2.65 (m, 4H), 1.88 (s, 3H), 1.68-1.72 (m, 4H), 1.47-1.51 (m, 3H), 1.30-1.33 (m, 1H);

RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.11 min.;

25 MS: MH^+ 528.

Example 495 *Trans* N1-benzyl-2-{4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetamide

A suspension of *trans* 2-{4-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetic acid (0.076 g, 0.000165 mol) in dichloromethane (2 mL) was reacted with triethylamine (0.050 g, 0.000496 mol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.063 g, 0.000248 mol). The mixture

was stirred two hours at ambient temperature, during which time dissolution occurred. The solution was washed with water (2 x 2 mL). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo*. The crude material was dissolved in dichloromethane (5 mL) and reacted with benzylamine (0.052 g, 0.000489 mol) at ambient temperature for 18 hours. The crude material was purified by flash column chromatography on silica using dichloromethane /methanol (95:5), followed by preparative RP-HPLC (Rainin C18, 8 μ m, 300 A, 25 cm; 60% isocratic for five minutes, then 60%-100% acetonitrile - 0.1M ammonium acetate over 20 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give trans *N*1-benzyl-2-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-hydroxycyclohexyl}acetamide as a white solid (0.010 g, 0.000018 mol).

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.53 (t, 1H) 8.24 (s, 1H), 7.66 (d, 2H), 7.43 (t, 2H), 7.09- 7.34 (m, 10H), 5.24 (s, 1H), 4.70-4.79 (m, 1H), 4.30 (d, 2H), 2.02-2.18 (m, 2H), 1.91 (s, 2H), 1.86-1.98 (m, 4H), 1.56-1.64 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min)

R_t 16.16 min.;

MS: MH⁺ 549.

20

Example 496 1-(Aminomethyl)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclobutanol.

A solution of 3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclobutanone (0.150 g, 0.000404 mol) in dichloromethane (5 mL) was reacted with 1,1,1-trimethylsilyl cyanide (0.060 g, 0.000606 mol) and anhydrous zinc iodide (0.004 g, 0.000012 mol). The mixture was stirred eight hours at reflux temperature. The mixture was partitioned between water (20 mL) and diethyl ether (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (10 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo*, and the crude material was dissolved in anhydrous tetrahydrofuran (10 mL) and reacted with lithium aluminum hydride (0.031 g, 0.000804 mol) at ambient temperature for 18 hours. The crude

material was purified by preparative RP-LC/MS (Gilson-Micromass C18, 5 μ m, 130A, 21 cm, 0%-100% acetonitrile-0.1M ammonium acetate over 9 min, 25 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give a 4:1 mixture of isomers of 1-(aminomethyl)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclobutanol as a white solid (0.024 g, 0.000060 mol).

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.24 (s, 1H) minor, 8.23 (s, 1H) major, 7.66-7.70 (m, 2H), 7.41-7.46 (m, 2H), 7.11- 7.21 (m, 5H), 5.45-5.50 (m, 1H) minor, 4.87-4.96 (m, 1H) major, 4.30 (d, 2H), 2.34-2.72 (m, 6H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.07 min.(minor) and 12.36 min (major); MS: MH⁺ 403.

Intermediate 1: 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)benzaldehyde

A mixture of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3.00 g, 11.5 mmol) and sodium hydride (60%, 0.506 g, 12.6 mmol) in DMF (50 mL) was stirred at ambient temperature for 1 h then 4-fluorobenzaldehyde (1.36 mL, 12.6 mmol) was added. The reaction mixture was heated at 100 °C for 21 h. The reaction mixture was cooled to ambient temperature and the precipitate was collected by filtration, washed with DMF (30 mL) and ether (30 mL), and dried to afford 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)benzaldehyde as a tan solid (2.80 g, 7.61 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δ H 10.03 (1H, s), 8.46 (2H, d, J = 8.4 Hz), 8.39 (1H, s), 8.09 (2H, d, J = 8.8 Hz); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 9.71 min. MS: MH⁺ 365.8.

Intermediate 2: N1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)benzaldehyde (0.400 g, 1.09 mmol), N1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide (0.735 g, 1.20

mmol), palladium tetrakis(triphenylphosphine) (0.127 g, 0.110 mmol), and sodium carbonate (0.279 g, 2.63 mmol) in DME (10 mL) and water (10 mL) was heated at 85 °C for 1 h. Additional *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide (0.026 g, 0.059 mmol) was added and the reaction mixture was heated at 85 °C for 4 h. The reaction mixture was cooled to ambient temperature and filtered. The residual solid was washed with methanol (50 mL) and DMF (50 mL), and the combined filtrates were concentrated to afford *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a beige solid (0.402 g, 0.730 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 10.05 (1H, s), 9.96 (1H, d, J = 4.0 Hz), 8.62 (1H, d, J = 8.4 Hz), 8.46 (1H, s), 8.39 (1H, d, J = 6.8 Hz), 8.12 (2H, d, J = 8.8 Hz), 8.02-8.03 (1H, m), 7.84-8.00 (1H, m), 7.75-7.77 (1H, m), 7.51 (1H, s), 7.43 (1H, d, J = 8.0 Hz), 3.97 (3H, s); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 12.46 min. MS: MH⁺ 551.2.

Intermediate 3: 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-ethanol

To a solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 19.1 mmol) in DMF (40 mL) was added sodium hydride (60%, 1.53 g, 38.3 mmol) and the reaction mixture was stirred for 20 min. 2-Bromoethanol (1.50 mL, 21.1 mmol) was added and the reaction mixture was heated at 50 °C for 18 h. The reaction mixture was cooled to ambient temperature and concentrated to afford a brown sludge. Ice water (50 mL) was added and the resulting precipitate was collected by filtration, rinsed with water (50 mL) and ether (50 mL), and dried in vacuo to afford 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-ethanol as a beige solid (4.30 g, 14.1 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 8.19 (1H, s), 4.84 (1H, t, J = 5.8 Hz), 4.30 (1H, t, J = 5.8 Hz), and 3.77 (2H, app q, J = 5.6 Hz); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 7.35 min.

Intermediate 4: 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-

indolyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-1-yl]ethyl methanesulfonate

To a 0 °C mixture of *N*2-{4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.343 g,
5 0.750 mmol) and pyridine (7.5 mL) was added methanesulfonyl chloride (0.14 mL,
1.8 mmol) dropwise over 30 sec. The reaction mixture was stirred at 0 °C for 2 h
then ice water (10 mL) was added. The precipitate was collected by filtration and
dried in vacuo to afford 2-[4-amino-3-(3-methoxy-4-{[(1-methyl-1*H*-2-
indolyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl
10 methanesulfonate as a beige solid (0.268 g, 0.500 mmol): ¹H NMR (d₆-DMSO, 400
MHz): δH 9.44 (1H, s), 8.30 (1H, s), 8.13 (1H, d, *J* = 8.0 Hz), 7.70 (1H, d, *J* = 8.0
Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.31-7.38 (4H, m), 7.15 (1H, t, *J* = 7.6 Hz), 4.70 (3H,
s), 4.04 (3H, s), 3.96 (3H, s), 3.37 (2H, obscured by water peak), and 3.12 (2H, s);
RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M
15 ammonium acetate over 15 min, 1 mL/min). *R*_t 11.22 min. MS: *M*+ 536.2.

Example 497: *N*1-(4-{4-amino-1-[4-(morpholinomethyl)phenyl]-1*H*-pyrazolo[3,4-
d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-
(trifluoromethyl)benzamide

20 A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide
(Intermediate 2) (0.075 g, 0.14 mmol), morpholine (0.024 mL, 0.27 mmol), and
sodium triacetoxyborohydride (0.087 g, 0.409 mmol) in dichloroethane (1.4 mL)
was shaken at ambient temperature for 16 h. Additional portions of morpholine
25 (0.012 mL, 0.14 mmol), sodium triacetoxyborohydride (0.043 g, 0.20 mmol), and
acetic acid (0.016 mL) were added and the reaction mixture was stirred at ambient
temperature for 24 h. 1 N NaOH (1 mL) was added and the reaction mixture was
filtered to afford a gray solid which was purified by preparative RP-HPLC (Rainin
C18, 8 μm, 300 Å, 25 cm; 10-60% acetonitrile - 0.05 M ammonium acetate over 25
30 min, 21 mL/min); the fraction eluting from 21-23 min was collected, concentrated,
and lyophilized to afford *N*1-(4-{4-amino-1-[4-(morpholinomethyl)phenyl]-1*H*-
pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-

(trifluoromethyl)benzamide as a white solid (0.007 g, 0.011 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δH 9.93 (1H, s), 8.34-8.37 (2H, m), 8.14-8.18 (2H, m), 7.97-8.02 (1H, m), 7.87-7.91 (1H, m), 7.73-7.76 (1H, m), 7.45-7.51 (2H, m), 7.44 (1H, s), 7.38-7.43 (1H, m), 3.41-3.59 (8H, m), and 3.36 (2H, s); RP-HPLC (Hypersil C18, 5 μm , 100 \AA , 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 11.72 min. MS: MH^+ 622.2.

Example 498: *N*1-[4-(4-amino-1-{4-[(4-hydroxypiperidino)methyl]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide monoacetate

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), 4-hydroxypiperidine (0.028 g, 0.27 mmol), and sodium triacetoxymethylborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at ambient temperature for 16 h. Additional portions of 4-hydroxypiperidine (0.028 g, 0.27 mmol) and acetic acid (0.016 mL) were added and the reaction mixture was shaken for 24 h. More 4-hydroxypiperidine (0.033 g, 0.33 mmol) and sodium triacetoxymethylborohydride (0.040 g, 0.19 mmol) were added and the reaction mixture was shaken for 72 h. 1N NaOH (1.5 mL) was added and the yellow-brown precipitate was collected by filtration and purified by preparative RP-HPLC (Rainin C18, 8 μm , 300 \AA , 25 cm; 10-60% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 21-23 min was collected, concentrated, and lyophilized to afford *N*1-[4-(4-amino-1-{4-[(4-hydroxypiperidino)methyl]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide monoacetate as a white solid (0.025 g, 0.039 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δH 9.95 (1H, s), 8.35-8.99 (2H, m), 8.14-8.19 (2H, m), 7.99-8.03 (1H, m), 7.89-7.93 (1H, m), 7.75-7.80 (1H, m), 7.39-7.51 (4H, m), 4.55 (1H, s), 3.96 (3H, s), 3.80 (2H, s), 2.68-2.71 (3H, m), 2.04-2.11 (2H, m), 1.85 (3H, s), 1.71-1.76 (2H, m), and 1.39-1.45 (2H, m); RP-HPLC (Hypersil C18, 5 μm , 100 \AA , 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.56 min. MS: MH^+ 636.2.

Example 499: *N*1-{4-[4-amino-1-(4-{[4-(2-hydroxyethyl)piperazino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

5 A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), *N*-(2-hydroxyethyl)piperazine (0.035 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 14 h. Additional portions of *N*-(2-hydroxyethyl)piperazine (0.010 g, 0.077 mmol) and sodium triacetoxyborohydride (0.020 g, 0.094 mmol) were added and the reaction mixture was shaken for 16 h. 1*N* NaOH (1.5 mL) was added and the precipitate was collected by filtration and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 10-60% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 21.9-22.9 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[4-(2-hydroxyethyl)piperazino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.034 g, 0.051 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δ H 9.94 (1H, s), 8.35-8.37 (2H, m), 8.15 (2H, d, *J* = 8.8 Hz), 8.00 (1H, t, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 10.4 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.49 (1H, s), 7.46 (2H, d, *J* = 7.2 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 3.96 (3H, s), 3.51 (2H, s), 3.46-3.49 (4H, m), and 2.35-2.44 (8H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 10.92 min. MS: *M*H⁺ 664.7.

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Example 500: *N*1-{4-[4-amino-1-(4-{[4-(2-hydroxyethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide diacetate

30 A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (0.075 g, 0.14 mmol), 4-piperidineethanol (0.035 g, 0.27 mmol), sodium

triacetoxyborohydride (0.087 g, 0.41 mmol), and dichloroethane (1.4 mL) was shaken at room temperature for 16 h. Additional portions of 4-piperidineethanol (0.040 g, 0.31 mmol) and sodium triacetoxyborohydride (0.053 g, 0.25 mmol) were added and the reaction mixture was shaken for 4 days. 1N NaOH (1 mL) was added and the precipitate was collected by filtration and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 10-60% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 21.1-23.5 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[4-(2-hydroxyethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide diacetate as a white solid. (0.015 g, 0.023 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δ H 9.94 (1H, s), 8.18-8.39 (2H, m), 8.14 (2H, d, *J* = 8.4 Hz), 7.99-8.02 (1H, m), 7.90 (1H, d, *J* = 10.4 Hz), 7.75 (1H, d, *J* = 7.6 Hz), 7.39-7.48 (4H, m), 4.31-3.96 (3H, s), 3.37 (2H, s), 3.37-3.50 (3H, m), 2.80-2.83 (2H, m), 1.91 (6H, m), 1.61-1.64 (2H, m), 1.35-1.37 (3H, m), and 1.15-1.18 (2H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 10.71 min. MS: MH⁺ 664.2.

Example 501: *N*1-{4-[4-amino-1-(4-{[3-(hydroxymethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide monoacetate

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), 3-piperidinemethanol (0.031 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 16 h. Additional 3-piperidinemethanol (0.045 g, 0.39 mmol) and sodium triacetoxyborohydride (0.090 g, 0.42 mmol) were added and the reaction mixture was shaken at ambient temperature for 16 h. 1N NaOH (1 mL) was added and the precipitate was collected by filtration and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 10-60% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 21-23 min

was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[3-(hydroxymethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide monoacetate as a white solid. (0.007 g, 0.11 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.95 (1H, s),
5 8.35-8.39 (2H, m), 8.14-8.17 (2H, m), 8.01-8.03 (1H, m), 7.89-7.93 (1H, m), 7.75-7.78 (1H, m), 7.40-7.50 (4H, m), 4.39-4.42 (1H, m), 3.97 (3H, s), 3.39-3.53 (3H, m), 3.01-3.21 (1H, m), 2.87-2.89 (1H, m), 2.75-2.77 (1H, m), 1.91 (3H, s), 1.61-1.65 (4H, m), 1.47-1.52 (1H, m), and 0.89-0.92 (1H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1
10 mL/min). R_t 10.73 min. MS: MH⁺ 650.2.

Example 502: *N*1-{4-[4-amino-1-(4-{[2-(hydroxymethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide monoacetate
15

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (0.075 g, 0.14 mmol), 2-piperidinemethanol (0.031 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken
20 at room temperature for 16 h. Additional portions of 2-piperidinemethanol (0.031 g, 0.27 mmol) and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) were added and the reaction mixture was shaken for 3 days. Again, 2-piperidinemethanol (0.030 g, 0.26 mmol) and sodium triacetoxyborohydride (0.073 g, 0.34 mmol) were added followed by acetic acid (0.1 mL). The reaction mixture was shaken for 5 days. 1N
25 NaOH (1 mL) was added and the reaction mixture was concentrated in vacuo to remove the dichloroethane. The residue was dissolved in DMF (2 mL), filtered through an Acrodisc syringe-tip filter, and purified by preparative RP-HPLC (Rainin C18, 8 μm, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 14.6-17.0 min was collected,
30 concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[2-(hydroxymethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide monoacetate as a white

solid. (0.026 g, 0.040 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δH 9.91 (1H, s), 8.33-8.37 (2H, m), 8.09-8.14 (2H, m), 7.96-8.00 (1H, m), 7.86-7.89 (1H, m), 7.71-7.74 (1H, m), 7.37-7.52 (4H, m), 4.46 (1H, bs), 4.10-4.15 (1H, m), 3.94 (3H, s), 3.64-3.67 (1H, m), 3.44-3.48 (1H, m), 2.64-2.69 (2H, m), 2.00-2.07 (1H, m), 1.94 (3H, s), 1.60-1.89 (2H, m), and 1.20-1.40 (4H, m); RP-HPLC (Hypersil C18, 5 μm , 100 \AA , 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.59 min. MS: MH^+ 649.7.

Example 503: *N*1-{4-[4-amino-1-(4-{[(2-morpholinoethyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), *N*-(2-aminoethyl)morpholine (0.035 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken for 16 h at room temperature. Additional portions of *N*-(2-aminoethyl)morpholine (0.030 mL, 0.23 mmol) and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) were added and the reaction mixture was shaken for 4 days. 1*N* NaOH (1 mL) was added and the precipitate was collected by filtration and purified by preparative RP-HPLC (Rainin C18, 8 μm , 300 \AA , 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 16.6-19.0 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[(2-morpholinoethyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid. (0.014 g, 0.021 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δH 9.88 (1H, s), 8.29-8.93 (2H, m), 8.11-8.17 (2H, m), 7.92-7.97 (1H, m), 7.83-7.86 (1H, m), 7.68-7.72 (1H, m), 7.46-7.51 (2H, m), 7.39 (1H, s), 7.34-7.38 (1H, m), 3.90 (3H, s), 3.50-3.52 (4H, m), 2.61-2.62 (2H, m), 2.40-2.50 (2H, obscured by DMSO peak), and 2.27-2.40 (6H, m); RP-HPLC (Hypersil C18, 5 μm , 100 \AA , 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.96 min. MS: MH^+ 665.2.

Example 504: *N*1-{4-[4-amino-1-(4-{[4-(hydroxymethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide diacetate

5 A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (0.075 g, 0.14 mmol), 4-piperidinemethanol (0.031 g, 0.27 mmol), and sodium triacetoxymethylborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of 4-piperidinemethanol (0.096 g, 0.83 mmol) and sodium triacetoxymethylborohydride (0.085 g, 0.40 mmol) were added
10 followed by acetic acid (0.1 mL). The reaction mixture was shaken for 5 days. 1*N* NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, then purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 17.2-18.3 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[4-(hydroxymethyl)piperidino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide diacetate as a white solid (0.018 g, 0.028 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δ H 9.94 (1H, s), 8.35-8.37 (2H, m), 8.14 (2H, d, *J* = 8.4 Hz), 8.00 (1H, t, *J* = 7.0 Hz), 7.90 (1H, d, *J* = 10.4 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.39-7.64 (4H, m), 4.38-4.41 (1H, m), 3.96 (3H, s), 3.50 (2H, s), 2.83 (2H, d, *J* = 10.8 Hz), 1.90 (6H, s), 1.63 (2H, d, *J* = 11.6 Hz), 1.34-1.35 (2H, m), and 1.12-1.19 (2H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 10.41
20 min. MS: MH⁺ 650.2.

Example 505: *N*1-{4-[4-amino-1-(4-{[4-(2-methoxyethyl)piperazino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide
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A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

(Intermediate 2) (0.075 g, 0.14 mmol), 1-(2-methoxyethyl)-piperazine (0.039 g, 0.27 mmol), and sodium triacetoxymethylborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of 1-(2-methoxyethyl)-piperazine (0.10 mL) and sodium triacetoxymethylborohydride (0.089 g, 0.41 mmol) were added and the reaction mixture was shaken for 16 h. 1N NaOH (1 mL) was added and the resulting solution was extracted with two portions of dichloromethane (2 mL each). The combined organic portions were concentrated to afford a brown solid which was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 16.9-20.2 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[4-(2-methoxyethyl)piperazino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.021 g, 0.031 mmol): ¹H NMR (*d*₆-DMSO, 400 MHz): δ H 9.94 (1H, s), 8.34-8.37 (2H, m), 8.14-8.17 (1H, m), 7.98-8.02 (1H, m), 7.89 (1H, d, *J* = 10.4 Hz), 7.74-7.76 (1H, m), 7.34-7.64 (6H, m), 3.96 (3H, s), 3.51 (2H, s), 3.31-3.43 (2H, m), 3.22 (3H, s), and 2.41-2.45 (10H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 11.24 min. MS: MH⁺ 678.7.

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Example 506: *N*1-{4-[4-amino-1-(4-{[(3*R*)-3-hydroxytetrahydro-1*H*-1-pyrrolyl]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (0.075 g, 0.14 mmol), (S)-3-hydroxypyrrolidine (0.024 g, 0.27 mmol), and sodium triacetoxymethylborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of (S)-3-hydroxypyrrolidine (0.1 mL) and sodium triacetoxymethylborohydride (0.084 g, 0.40 mmol) were added and the reaction mixture was shaken for 3 days. Acetic acid (0.1 mL) was added and the reaction mixture was shaken for 4 days. 1N NaOH (1 mL) was added and the reaction mixture was concentrated in vacuo. The residue was dissolved in DMF (2

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mL), filtered through a syringe-tip Acrodisc filter, and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 16.5-18.4 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[(3*R*)-3-hydroxytetrahydro-1*H*-1-pyrrolyl]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.027 g, 0.043 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.89 (1H, s), 8.30-8.33 (2H, m), 8.13-8.14 (2H, m), 7.90-7.80 (1H, m), 7.84 (1H, d, J = 10.8 Hz), 7.70 (1H, d, J = 7.6 Hz), 7.35-7.59 (4H, m), 4.64 (1H, bs), 4.14-4.23 (1H, m), 3.91 (3H, s), 3.62 (2H, s), 2.61-2.62 (2H, m), 2.27-2.28 (2H, m), 2.27-2.28 (2H, m), 2.02 (1H, m), and 1.60 (1H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.41 min. MS: MH⁺ 622.2.

Example 507: *N*1-{4-[4-amino-1-(4-{[(3*R*)-3-hydroxytetrahydro-1*H*-1-pyrrolyl]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), (R)-(+)-3-pyrrolidinol (0.024 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of (R)-(+)-3-pyrrolidinol (0.1 mL), and sodium triacetoxyborohydride (0.084 g, 0.40 mmol) were added and the reaction mixture was shaken for 16 h. 1N NaOH (1 mL) was added and the precipitate was collected by filtration and combined with the residue obtained from extraction of the water layer with one portion of dichloromethane (20 mL). The crude mixture was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min). The appropriate fraction was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[(3*R*)-3-hydroxytetrahydro-1*H*-1-pyrrolyl]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.034 g, 0.055 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.93 (1H, s), 8.34-8.37 (2H, m), 8.15-8.19 (2H,

m), 7.98-8.01 (1H, m), 7.85 (1H, d, J = 10.4 Hz), 7.75 (1H, d, J = 8.0 Hz), 7.48-7.54 (2H, m), 7.44 (1H, s), 7.40 (1H, d, J = 8.4 Hz), 4.70 (1H, bs), 4.22 (1H, s), 3.96 (3H, s), 3.63 (2H, s), 2.49-2.72 (3H, m), 2.13-2.41 (1H, m), 1.91-2.06 (1H, m), and 1.53-1.61 (1H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.53 min. MS: MH+ 622.2.

Example 508: *N*1-(4-{4-amino-1-[4-({[3-(1*H*-1-imidazolyl)propyl]amino}methyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), 1-(3-aminopropyl)imidazole (0.034 g, 0.27 mmol), and sodium triacetoxymethylborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of 1-(3-aminopropyl)imidazole (0.1 mL) and sodium triacetoxymethylborohydride (0.086 g, 0.40 mmol) were added and the reaction mixture was shaken for 3 days. Acetic acid (0.1 mL) was added and the reaction mixture was shaken for 4 days. 1*N* NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile – 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 14.0-15.7 min was collected, concentrated, and lyophilized to afford *N*1-(4-{4-amino-1-[4-({[3-(1*H*-1-imidazolyl)propyl]amino}methyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.040 g, 0.061 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δ H 9.94 (1H, s), 8.35-8.40 (2H, m), 8.16 (2H, d, J = 7.6 Hz), 7.99 (1H, t, J = 7.6 Hz), 7.89 (1H, d, J = 10.0 Hz), 7.75 (1H, d, J = 8.4 Hz), 7.59 (1H, s), 7.52 (2H, d, J = 3.8 Hz), 6.45 (1H, s), 7.40 (1H, d, J = 8.0 Hz), 7.16 (1H, s), 6.87 (1H, s), 4.04 (2H, t, J = 7.0 Hz), 3.96 (3H, s), 3.77 (2H, s), 2.45-2.46 (2H, m), 1.91 (3H, s), and 1.86-1.90 (2H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min,

1 mL/min). R_t 10.28 min. MS: MH+ 660.2.

Example 509: *N*1-{4-[4-amino-1-(4-{[(4-hydroxybutyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), 4-amino-1-butanol (0.024 g, 0.27 mmol), and sodium triacetoxymethylborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken for 3 days. Additional portions of 4-amino-1-butanol (0.1 mL) and sodium triacetoxymethylborohydride (0.089 g, 0.42 mmol) were added and the reaction mixture was shaken for 3 days. Acetic acid (0.1 mL) was added and the reaction mixture was shaken for 7 days. An additional portion of sodium triacetoxymethylborohydride (0.098 g, 0.46 mmol) was added and the reaction mixture was shaken for 16 h. 1*N* NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 12.5-14.8 min was collected, concentrated, and lyophilized to *N*1-{4-[4-amino-1-(4-{[(4-hydroxybutyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid. (0.030 g, 0.048 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δ H 9.94 (1H, d, J = 4.4 Hz), 8.35-8.40 (2H, m), 8.17 (2H, d, J = 8.0 Hz), 8.00 (1H, t, J = 7.4 Hz), 7.90 (1H, d, J = 10.4 Hz), 7.75 (1H, d, J = 7.2 Hz), 7.53-7.57 (2H, m), 7.45 (1H, s), 7.40 (1H, d, J = 8.8 Hz), 3.96 (3H, s), 3.83 (2H, s), 3.39 (2H, t, J = 6.2 Hz), 2.45-2.50 (2H, m), and 1.45-1.51 (4H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 9.93 min. MS: MH+ 624.3.

Example 510: *N*1-{4-[4-amino-1-(4-{[(3-methoxypropyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), 3-methoxypropylamine (0.024 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of 3-methoxypropylamine (0.1 mL, 1 mmol) and sodium triacetoxyborohydride (0.085 g, 0.40 mmol) were added and the mixture was shaken for 3 days. Acetic acid (0.1 mL) was added and the reaction mixture was shaken for 4 days. An additional portion of sodium triacetoxyborohydride (0.100 g, 0.470 mmol) was added and the reaction mixture was shaken for 16 h. 1*N* NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 18.0-19.7 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[(3-methoxypropyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.009 g, 0.014 mmol): ¹H NMR (*d*₆-DMSO, 400 MHz): δ H 9.93 (1H, s), 8.33-8.38 (2H, m), 8.18-8.20 (2H, m), 7.97-8.01 (1H, m), 7.87-7.91 (1H, m), 7.73-7.76 (1H, m), 7.54-7.64 (5H, m), 7.31-7.45 (2H, m), 3.95 (3H, s), 3.85-3.89 (2H, m), 3.38 (2H, s), 2.55-2.68 (2H, m), and 1.70-1.74 (2H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 10.58 min. MS: MH⁺ 624.2.

Example 511: *N*1-(4-{4-amino-1-[4-({[(3-(dimethylamino)propyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide monoacetate

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), *N,N*-dimethyl-1,3-propane diamine (0.028 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in

dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of N,N-dimethyl-1,3-propane diamine (0.1 mL) and sodium triacetoxyborohydride (0.085 g, 0.40 mmol) were added and the mixture was shaken for 3 days. Acetic acid (0.1 mL) was added and the mixture was shaken for 4 days.

5 Sodium triacetoxyborohydride (0.096 g, 0.45 mmol) was added and the mixture was shaken for 16 h. 1N NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction

10 eluting from 14.3-14.9 min was collected, concentrated, and lyophilized to afford N1-(4-{4-amino-1-[4-{([3-(dimethylamino)propyl]amino)methyl}phenyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide monoacetate as a white solid (0.020 g, 0.031 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δ H 9.93 (1H, s), 8.34-8.37 (2H, m), 8.13 (2H, d, J = 8.4 Hz), 8.00 (1H, t, J = 7.2 Hz), 7.89 (1H, d, J = 10.0 Hz), 7.75 (1H, d, J = 7.6 Hz), 7.49 (2H, d, J = 8.0 Hz), 7.44 (1H, s), 7.39 (1H, d, J = 8.0 Hz), 3.96 (3H, s), 3.74 (2H, s), 2.21-2.25 (2H, t, J = 7.0 Hz), 2.09 (6H, s), 2.08 (3H, s), 1.86-1.87 (4H, m), and 1.54-1.58 (2H, t, J = 7.2 Hz); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.85

20 min. MS: MH⁺ 637.3.

Example 512: Methyl (2S)-2-({4-[4-amino-3-(4-{[2-fluoro-4-(trifluoromethyl)benzoyl]amino}-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]benzyl}amino)-3-(4H-4-imidazolyl)propanoate

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A mixture of N1-{4-[4-amino-1-(4-formylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), L-histidine methyl ester dihydrochloride (0.046 g, 0.27 mmol), and sodium triacetoxyborohydride (0.087 g, 0.41 mmol) in

30 dichloroethane (1.4 mL) was shaken at room temperature for 3 days. Additional portions of), L-histidine methyl ester dihydrochloride (0.100 g, 0.59 mmol) and sodium triacetoxyborohydride (0.085 g, 0.40 mmol) were added and the reaction

mixture was shaken for 2 days. 1N NaOH (1 mL) was added and the brown precipitate was collected by filtration. The filtrate was extracted with dichloromethane (5 mL) and the organic extract was concentrated and combined with the aforementioned brown solid. The crude mixture was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 18.9-20.5 min was collected, concentrated, and lyophilized to afford methyl (2*S*)-2-({4-[4-amino-3-(4-{[2-fluoro-4-(trifluoromethyl)benzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}amino)-3-(4*H*-4-imidazolyl)propanoate as a white solid. (0.029 g, 0.041 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δ H 9.94 (1H, s), 8.35-8.38 (2H, m), 8.13 (2H, d, *J* = 8.0 Hz), 7.99-8.02 (1H, m), 7.90 (1H, d, *J* = 10.8 Hz), 7.75 (1H, d, *J* = 8.4 Hz), 7.51 (1H, s), 7.39-7.45 (5H, m), 6.78 (1H, bs), 3.96 (3H, s), 3.82 (1H, d, *J* = 14.0 Hz), 3.59 (3H, s), 3.47 (1H, t, *J* = 6.4 Hz), 2.80-2.89 (2H, m), and 1.91 (3H, s); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile - 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 11.15 min. MS: MH⁺ 704.2.

Example 513: *N*1-{4-[4-amino-1-(4-{[(2-methoxyethyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.075 g, 0.14 mmol), 2-methoxyethylamine (0.018 g, 0.24 mmol), and sodium triacetoxyborohydride (0.106 g, 0.500 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 24 h. 1N NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, and purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 15.0-16.2 min was collected, concentrated, and lyophilized to afford *N*1-{4-[4-amino-1-(4-{[(2-methoxyethyl)amino]methyl}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.010 g,

0.016 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δH 9.94 (1H, d, $J = 4.0$ Hz), 8.35-8.37 (2H, m), 8.16 (2H, d, $J = 8.0$ Hz), 8.01 (1H, t, $J = 7.4$ Hz), 7.90 (1H, d, $J = 10.0$ Hz), 7.75 (1H, d, $J = 8.0$ Hz), 7.52 (2H, d, $J = 8.0$ Hz), 7.45 (1H, s), 7.40 (1H, d, $J = 8.8$ Hz), 3.96 (3H, s), 3.80 (2H, s), 3.42-3.45 (2H, m), 3.25 (2H, m), and 2.70-2.71 (2H, m); RP-HPLC (Hypersil C18, 5 μm , 100 \AA , 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.23 min. MS: MH^+ 610.2.

Example 514: *N*1-(4-{4-amino-1-[4-{([2-(dimethylamino)ethyl]amino)methyl}phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of *N*1-{4-[4-amino-1-(4-formylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 2) (0.080 g, 0.14 mmol), *N,N*-dimethylaminoethylamine (0.03 mL), and sodium triacetoxyborohydride (0.100 g, 0.472 mmol) in dichloroethane (1.4 mL) was shaken at room temperature for 24 h. 1N NaOH (1 mL) was added and the reaction mixture was concentrated, dissolved in DMF (2 mL), filtered through a syringe-tip Acrodisc filter, and purified by RP-HPLC (Rainin C18, 8 μm , 300 \AA , 25 cm; 20-80% acetonitrile - 0.05 M ammonium acetate over 25 min, 21 mL/min); the fraction eluting from 16.5-17.8 min was collected, concentrated, and lyophilized to afford *N*1-(4-{4-amino-1-[4-{([2-(dimethylamino)ethyl]amino)methyl}phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide as a white solid (0.020 g, 0.032 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δH 9.94 (1H, d, $J = 4.4$ Hz), 8.35-8.37 (2H, m), 8.15 (2H, d, $J = 8.4$ Hz), 8.01 (1H, t, $J = 7.8$ Hz), 7.90 (1H, d, $J = 10.4$ Hz), 7.75 (1H, d, $J = 7.6$ Hz), 7.50 (2H, d, $J = 8.8$ Hz), 7.45 (1H, s), 7.40 (1H, d, $J = 8.0$ Hz), 3.96 (3H, s), 3.77 (2H, s), 2.59 (2H, t, $J = 6.6$ Hz), 2.35 (2H, t, $J = 6.6$ Hz), and 2.12 (6H, s); RP-HPLC (Hypersil C18, 5 μm , 100 \AA , 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.85 min. MS: MH^+ 623.2.

Example 515: *N*1-{4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-ethanol (Intermediate 3) (0.120 g, 0.393 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide (0.190 g, 0.433 mmol), palladium tetrakis(triphenylphosphine) (0.045 g, 0.039 mmol), and sodium carbonate (0.100 g, 0.943 mmol) in DME (3.9 mL) and water (3.9 mL) was heated at 85 °C for 3 h. The reaction mixture was cooled to ambient temperature and the organic solvent was removed in vacuo. The precipitate was collected by filtration, rinsed with water (20 mL) and ether (20 mL), and dried in vacuo to afford *N*1-{4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide as a brown solid (0.125 g, 0.254 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.89 (1H, d, *J* = 4.0 Hz), 8.31 (1H, d, *J* = 8.0 Hz), 8.25 (1H, s), 7.99 (1H, t, *J* = 7.4 Hz), 7.89 (1H, d, *J* = 10.4 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.34 (1H, s), 7.31 (1H, d, *J* = 8.4 Hz), 4.89 (1H, s), 4.40 (2H, t, *J* = 5.6 Hz), 3.94 (3H, s), and 3.86 (2H, t, *J* = 5.6 Hz); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 9.85 min. MS: *M*H⁺ 491.

Example 516: *N*2-{4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A mixture of 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-ethanol (Intermediate 3) (0.364 g, 1.19 mol), *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.485 g, 1.19 mmol), palladium tetrakis(triphenylphosphine) (0.138 g, 0.119 mmol), and sodium carbonate (0.303 g, 2.86 mmol) in DME (12 mL) and water (12 mL) was heated at 85 °C for 4 h then cooled to ambient temperature. The DME was removed in vacuo and the resulting precipitate was collected by filtration and rinsed with water (50 mL) and ether (50 mL) to afford *N*2-{4-[4-amino-1-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide as a tan solid (0.459 g, 1.00 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.44 (1H, s), 8.26 (1H, s), 8.12 (1H, d, *J* = 8.0 Hz), 7.70 (1H, d, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.29-7.41 (6H, m), 7.15 (1H, t, *J* = 7.4 Hz), 4.90 (1H, t, *J* = 5.8 Hz), 4.41 (2H, t, *J* = 5.8 Hz), 4.04 (3H, s), 3.96 (3H, s), and 3.86 (2H, q, *J* =

5.9 Hz); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.52 min. MS: MH^+ 458.2.

Example 517: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide trimaleate

A mixture of 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.265 g, 0.495 mmol), *N*-methylpiperazine (0.065 mL, 0.58 mmol), and triethylamine (0.10 mL, 0.74 mmol) in DMF (5 mL) was heated at 70 °C for 20 h. The reaction mixture was cooled to ambient temperature and the solvent removed in vacuo. Water (25 mL) was added and the resulting precipitate was collected by filtration, washed with water (25 mL) and ether (50 mL), and dried in vacuo to afford a brown solid which was purified by silica gel column chromatography. The appropriate fractions were combined and concentrated to afford *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide as a beige solid (0.084 g, 0.16 mmol): 1H NMR (d_6 -DMSO, 400 MHz): δ H 9.44 (1H, s), 8.26 (1H, s), 8.11 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.29-7.35 (4H, m), 7.15 (1H, t, J = 7.4 Hz), 4.46 (2H, t, J = 6.8 Hz), 4.04 (3H, s), 3.96 (3H, s), 2.80 (2H, t, J = 6.6 Hz), 2.49-2.50 (2H, obscured by DMSO peak), 2.23-2.26 (4H, m), 2.12 (3H, s), and 0.97-0.99 (2H, m); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.24. MS: MH^+ 540.3.

To a mixture of *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.082 g, 0.15 mmol) in warm ethyl acetate (2 mL) was added a solution of maleic acid (0.053 g, 0.46 mmol) in warm ethyl acetate (1 mL). A precipitate formed immediately. The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration, washed with ethyl acetate (5 mL), and dried in vacuo to afford *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-

methyl-1*H*-2-indolecarboxamide trimaleate as a beige solid (0.090 g, 0.10 mmol):

¹H NMR (d₆-DMSO, 400 MHz): δH 9.45 (1H, s), 8.27 (1H, s), 8.12 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 8.0 Hz), 7.59 (1H, d, J = 8.0 Hz), 7.29-7.36 (4H, m), 7.15 (1H, t, J = 7.4 Hz), 6.17 (6H, s), 4.50 (2H, t, J = 6.4 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.10-3.20 (4H, m), 2.92-2.95 (4H, m), 2.74 (3H, s), and 2.32-2.37 (2H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.48 min. MS: M⁺ 540.3.

Example 518: *N*2-{4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide dimaleate

To a mixture of 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.200 g, 0.373 mmol), triethylamine (0.052 mL, 0.37 mmol), and sodium iodide (0.056 g, 0.37 mmol) in DMF (5 mL) was added morpholine (0.039 mL, 0.45 mmol). The reaction mixture was heated at 60 °C for 60 h. Morpholine (0.100 mL, 1.15 mmol) was added and the reaction mixture was heated at 80 °C for 30 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Water (5 mL) was added and the resulting precipitate was collected by filtration, washed with water (5 mL) and ether (10 mL), and dried in vacuo to afford a tan solid which was purified twice by silica gel chromatography (elution with 20% MeOH-CH₂Cl₂); the appropriate fractions were combined and concentrated to afford a beige solid which was triturated from ether and dried in vacuo to afford *N*2-{4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide as a white solid (0.048 g, 0.054 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.44 (1H, s), 8.26 (1H, s), 8.11 (1H, d, J = 8.0 Hz), 7.70 (1H, d, J = 7.6 Hz), 7.58 (1H, d, J = 7.6 Hz), 7.29-7.35 (4H, m), 7.15 (1H, t, J = 7.6 Hz), 4.48 (2H, t, J = 6.4 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.50-3.53 (4H, m), 2.82 (2H, t, J = 6.2 Hz), and 2.47-2.51 (4H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.02 min. MS: M⁺ 527.3.

To a mixture of *N*2-{4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-

d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.048 g, 0.091 mmol) in warm ethyl acetate (2 mL) was added a solution of maleic acid (0.021 g, 0.18 mmol) in warm ethyl acetate (1 mL). A precipitate formed immediately. The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration, washed with ethyl acetate (5 mL), and dried in vacuo to afford *N*2-[4-[4-amino-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide dimaleate as a light brown solid (0.030 g, 0.039 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.45 (1H, s), 8.31 (1H, s), 8.15 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.31-7.35 (4H, m), 7.16 (1H, t, *J* = 7.4 Hz), 6.17 (4H, s), 4.72-4.73 (2H, m), 4.04 (3H, s), 3.96 (3H, s), 3.72-3.79 (4H, m), and 3.10-3.30 (6H, obscured by water peak); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 11.08 min. MS: *M*+ 527.3.

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Example 519: *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]ethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide monomaleate

A mixture of 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.080 g, 0.15 mmol), ethanolamine (0.05 mL, 0.82 mmol), triethylamine (0.021 mL, 0.15 mmol), and sodium iodide (0.021 g, 0.15 mmol) in DMF (2.5 mL) was heated at 70 °C for 15 h. The reaction mixture was cooled to ambient temperature and concentrated; water (5 mL) was added and the resulting precipitate was collected by filtration and rinsed with water (5 mL). The crude solid was purified by silica gel column chromatography (elution with 20% MeOH-CH₂Cl₂). The appropriate fractions were combined and the solvent removed in vacuo to afford *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]ethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide as a white solid (0.009 g, 0.02 mmol). RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 9.39 min. MS: *M*+ 501.3.

To a warm solution of *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]ethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.009 g, 0.02 mmol) in ethyl acetate (2 mL) was added a solution of maleic acid (0.005 g, 0.04 mmol) in ethyl acetate (0.5 mL). The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration and dried in vacuo to afford *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]ethyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide monomaleate as a white solid (0.009 g, 0.014 mmol): ¹H NMR (d₆-DMSO, 400 MHz): δH 9.45 (1H, s), 8.69-8.74 (2H, bs), 8.31 (1H, s), 8.14 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.32-7.36 (4H, m), 7.15 (1H, t, *J* = 7.4 Hz), 6.07 (2H, s), 5.28 (1H, t, *J* = 4.2 Hz), 4.71 (2H, t, *J* = 5.8 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.65-3.67 (2H, m), 3.50-3.60 (2H, m), and 3.10-3.20 (2H, m); RP-HPLC (Hypersil C18, 5 μm, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). *R*_t 9.97 min. MS: *M*+ 501.3.

Example 520: *N*2-(4-{4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide monomaleate

A mixture of 2-[4-amino-3-(3-methoxy-4-{[(1-methyl-1*H*-2-indolyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.080 g, 0.15 mmol), dimethylamine (2.0 M in THF, 0.07 mL, 0.15 mmol), triethylamine (0.021 mL, 0.15 mmol), and sodium iodide (0.021 g, 0.15 mmol) in DMF (2.5 mL) was heated in a resealable tube at 70 °C for 15 h. Additional dimethylamine solution (0.10 mL) was added and the reaction mixture was heated at 70 °C for 20 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Water (5 mL) was added and the resulting precipitate was collected by filtration and purified by silica gel column chromatography (elution with 20% MeOH:CH₂Cl₂ to 10:30:60 Et₃N:MeOH:CH₂Cl₂); the appropriate fractions were combined and concentrated to afford *N*2-(4-{4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide as a white solid (0.009 g,

0.02 mmol). RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.52. MS: M^+ 485.2.

To a warm solution of *N*2-(4-{4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.009 g, 0.02 mmol) in ethyl acetate (2 mL) was added a solution of maleic acid (0.005 g, 0.04 mmol) in ethyl acetate (1 mL). The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration and dried in vacuo to afford *N*2-(4-{4-amino-1-[2-(dimethylamino)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide monomaleate as a white solid (0.005 g, 0.008 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δ H 9.46 (1H, s), 8.32 (1H, s), 8.15 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 7.6 Hz), 7.59 (1H, d, J = 8.4 Hz), 7.32-7.35 (4H, m), 7.16 (1H, t, J = 7.4 Hz), 6.06 (2H, s), 4.75 (2H, t, J = 6.0 Hz), 4.04 (3H, s), 3.96 (3H, s), 3.65 (2H, t, J = 5.6 Hz), and 2.88 (6H, s); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.08 min. MS: M^+ 485.2.

Example 521: *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide trimaleate

A mixture of 2-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)carbonyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl methanesulfonate (Intermediate 4) (0.080 g, 0.15 mmol), imidazole (0.011 g, 0.15 mmol), triethylamine (0.021 mL, 0.15 mmol), and sodium iodide (0.021 g, 0.15 mmol) in DMF (2.5 mL) was heated at 70 °C for 15 h. Imidazole (0.011 g, 0.15 mmol) was added and the reaction mixture was heated at 70 °C for 60 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Water (5 mL) was added and the resulting precipitate was collected by filtration to afford a beige solid which was taken up in hot ethyl acetate then allowed to slowly cool to ambient temperature. The filtrate was concentrated to afford *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.034 g, 0.067 mmol): RP-

HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.45 min. MS: M^+ 508.2.

To a warm mixture of *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.034 g, 0.067 mmol) in ethyl acetate (2 mL) was added a solution of maleic acid (0.016 g, 0.13 mmol) in ethyl acetate (1 mL); a white precipitate formed immediately. The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration and dried in vacuo to afford *N*2-(4-{4-amino-1-[2-(1*H*-1-imidazolyl)ethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide trimaleate as a yellow solid (0.011 g, 0.011 mmol): ^1H NMR (d_6 -DMSO, 400 MHz): δ H 9.44 (1H, s), 8.90 (1H, s), 8.20 (1H, s), 8.12 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 8.0 Hz), 7.58-7.63 (3H, m), 7.32-7.36 (2H, m), 7.24-7.26 (2H, m), 7.16 (1H, t, J = 7.6 Hz), 6.18 (6H, s), 4.85 (2H, t, J = 6.8 Hz), 4.71 (2H, t, J = 5.2 Hz), 4.04 (3H, s), and 4.00 (3H, s); RP-HPLC (Hypersil C18, 5 μ m, 100 Å, 15 cm; 5%-100% acetonitrile – 0.1 M ammonium acetate over 15 min, 1 mL/min). R_t 10.35 min. MS: M^+ 508.2.

Example 522: *N*1-{4-[4-Amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A solution of 2-fluoro-4-trifluoromethyl-1-benzenecarbonyl chloride (0.87 g, 3.83 mmol) in dichloromethane (5 mL) was added into a mixture of pyridine (15 mL) and 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclohexanone (1.00 g, 2.56 mmol) in dichloromethane (5 mL) at 0°C over 5 minutes. The mixture was stirred at 0°C for 10 minutes and at ambient temperature overnight. The solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane. The dichloromethane layer was washed with saturated aqueous ammonium chloride twice and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.95 g, 1.76 mmol) as a white solid: ^1H NMR

(DMSO-*d*₆, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.28 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.27 (m, 1H), 3.94 (s, 3H), 2.70 (m, 2H), 2.47 (m, 4H), 2.17 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 μ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 9.23 min. MS: MH⁺ 543.

Example 523: *Cis-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide: and

10 Example 524: *Trans-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

Morpholine (0.08 mL, 0.93 mmol) was added into a mixture of *N1*-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (Example 522) (0.42 g, 0.78 mmol) and acetic acid (0.11 mL, 1.86 mmol) in dichloroethane (25 mL). The mixture was stirred at ambient temperature for 10 minutes. Sodium triacetoxyborohydride (0.23 g, 1.09 mmol) was added and the mixture was stirred at ambient temperature overnight. Water (6 mL) was added followed by sodium bicarbonate (0.38 g, 4.53 mmol). The mixture was stirred for 1 hour and the organic layer was separated. The aqueous layer was extracted with dichloromethane (20 mL). The combine organics were dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide *cis-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.37 mmol) and *trans-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.09 g, 0.14 mmol) as white solids.

30 Data for *cis-N1*-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide: ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.91 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H),

7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.83 (m, 1H), 3.94 (s, 3H), 3.62 (br, 4H), 1.57-2.55 (m, 10H); MS: MH⁺ 614.

Data for trans-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-
5 *d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide: ¹H
NMR (DMSO-*d*₆, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 7.99 (t, 1H),
7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 4.67 (m, 1H), 3.94 (s, 3H), 3.59
(br, 4H), 1.48-2.69 (m, 10H); MS: MH⁺ 614.

10 Example 525: Cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-
trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-1-yl]cyclohexyl}amino)propanoate; and

Example 526: Trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-
trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-
15 *d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate

A similar procedure to the preparation of cis-*N*1-{4-[4-amino-1-(4-
morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-
fluoro-4-trifluoromethylbenzamide and trans-*N*1-{4-[4-amino-1-(4-
morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-
20 fluoro-4-trifluoromethylbenzamide yielded cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-
4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-
1-yl]cyclohexyl}amino)propanoate and trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-
4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-
1-yl]cyclohexyl}amino)propanoate as white solids.

25 Data for cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-
3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate:
¹H NMR (DMSO-*d*₆, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.00 (t,
1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.37 (m,
30 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.76 (m, 2H), 2.32 (m, 2H), 1.88 (m, 2H), 1.67 (m,
4H), 1.16 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A,
250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min,

1mL/min) R_t 7.92 min. MS: MH^+ 644.

Data for trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate: 1H NMR (DMSO- d_6 , 400MHz) δ 9.89 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 4.68 (m, 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.82 (m, 2H), 2.46 (m, 5H), 1.91-2.07 (m, 6H), 1.18 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 μ m, 100A, 250x4.6mm, 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 7.69 min. MS: MH^+ 644.

Example 527: Cis-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid

15 A mixture of cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate (Example 525) (0.23 g, 0.36 mmol), p-dioxane (15 mL), potassium hydroxide (0.10 g, 1.81 mmol) and water (1.5 mL) were heated at 80°C for 3 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield cis-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid (0.11 g, 0.18 mmol) as a white solid: 1H NMR (DMSO- d_6 , 400MHz) δ 9.91 (dd, 1H), 8.31 (d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 6.89 (br, 2H), 4.79 (m, 1H), 3.95 (s, 20 3H), 2.46-3.00 (m, 7H), 2.29 (m, 2H), 1.91 (m, 2H), 1.80 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 μ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 6.06 min. MS: MH^+ 616.

Example 528: Trans-3-({4-[4-amino-3-(3-methoxy-4-{[2-methoxy-4-trifluoromethylbenzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid

A mixture of trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-

trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate (Example 526) (0.04 g, 0.06 mmol), p-dioxane (4 mL), potassium hydroxide (0.02 g, 0.31 mmol), a trace amount of methanol and water (0.4 mL) were heated at 80°C for 1 hour. The mixture was stirred at ambient temperature overnight and at 80°C for 4 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield trans-3-({4-[4-amino-3-(3-methoxy-4-{[2-methoxy-4-trifluoromethylbenzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid (0.04 g, 0.06 mmol) as a white solid: ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.72 (s, 1H), 8.61(d, 1H), 8.28 (d, 1H), 8.24 (s, 1H), 7.61(s, 1H), 7.53 (d, 1H), 7.33 (s, 1H), 7.29 (d, 1H), 4.72 (m, 1H), 4.20 (s, 3H), 4.05 (s, 3H), 1.44-3.61 (m, 13H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 μ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 6.36 min. MS: MH⁺ 628.

Example 529: *N*1-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide

A. *N*1-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide

A mixture of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.10 g, 0.19 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.13 g, 0.29 mmol), tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.01 mmol) and sodium carbonate monohydrate (0.06 mg, 0.48 mmol) in water (2 mL) and ethylene glycol dimethyl ether (4 mL) was heated at 85°C overnight. The solvents were removed under reduced pressure. Water was added into the residue and the mixture was extracted with ethyl acetate three times. The combined organics were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a brown solid which was purified by flash column chromatography on silica using Isco system to provide *N*1-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.12 g, 0.17 mmol) as a white solid: ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.89 (dd, 1H), 8.25(d, 1H), 8.28 (s, 1H), 8.00 (t, 1H), 7.94 (s, 1H), 7.88

(d, 1H), 7.73 (d, 1H), 7.24 (m, 15H), 3.90 (s, 3H); MS: MH^+ 689.

B. *N1*-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide

5 A mixture of *N1*-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (2.10 g, 1.75 mmol), 6 N aqueous hydrochloric acid (10 mL), p-dioxane (10 mL) and ethanol (8 mL) was heated at 50°C for 6 hours. The mixture was filtered and the solid was washed with ethanol, dried in a vacuum oven over the weekend, and purified by flash column
10 chromatography on silica to provide *N1*-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.35 g, 0.78 mmol). The filtrate was concentrated and purified by flash column chromatography on silica and preparative HPLC to provide the same product *N1*-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-
15 trifluoromethylbenzamide (0.67 g, 1.51 mmol) as a white solid: 1H NMR (DMSO-*d*₆, 400MHz) δ 13.58 (s, 1H), 9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.05 (t, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.36 (s, 1H), 7.24 (d, 1H), 3.94 (s, 3H); MS: MH^+ 447.

Example 530: *N1*-[4-(4-Amino-1-tetrahydro-2*H*-4-pyran-1*H*-pyrazolo[3,4-
20 *d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide

Diethyl azodicarboxylate (0.07 mL, 0.45 mmol) was added into a mixture of *N1*-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.10 g, 0.22 mmol), triphenylphosphine (0.12 g, 0.45
25 mmol) and tetrahydro-4*H*-pyran-4-ol (0.04 g, 0.34 mmol) in tetrahydrofuran (5 mL) and the mixture was stirred at ambient temperature overnight. Tetrahydro-4*H*-pyran-4-ol (0.01 g, 0.11 mmol), triphenylphosphine (0.04 g, 0.15 mmol) and diethyl azodicarboxylate (0.02 mL, 0.15 mmol) were added and the mixture was stirred at ambient temperature for 5 hours. The solvents were evaporated and the residue was
30 purified by preparative HPLC to yield *N1*-[4-(4-amino-1-tetrahydro-2*H*-4-pyran-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.03 g, 0.06 mmol) as a white solid: 1H NMR (DMSO-*d*₆, 400MHz) δ 9.91 (dd, 1H), 8.30(d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75

(d, 1H), 7.34 (s, 1H), 7.31 (d, 1H), 6.90 (br, 2H), 4.95 (m, 1H), 4.02 (m, 2H), 3.95 (s, 3H), 3.56 (t, 2H), 2.22 (m, 2H), 1.89 (m, 2H); MS: MH^+ 531.

Example 531: *N1*-{4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A. 4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol

10 A mixture of tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol), 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.30 g, 1.14 mmol) and dimethyl sulfoxide (3 mL) was stirred at ambient temperature in the dark for 2 minutes and cooled to 0°C. A solution of 2,4*a*-dihydro-1*aH*-cyclopenta[*b*]oxirene (0.14 g, 1.72 mmol) in tetrahydrofuran (3 mL) was added into the mixture at 0°C and stirred at
15 0°C for 3 hours. The mixture was stirred at ambient temperature overnight and purified by preparative HPLC to yield 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.24 g, 0.70 mmol) as a white solid: RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 4.23 min. MS:
20 MH^+ 344.

B. *N1*-{4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

25 A mixture of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.12 g, 0.35 mmol), *N1*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.53 mmol), tetrakis(triphenyl-phosphine)palladium(0) (0.02 g, 0.02 mmol) and sodium carbonate monohydrate (0.11 g, 0.88 mmol) was heated in a mixture of ethylene
30 glycol dimethyl ether (6 mL) and water (3 mL) at 85° C for 6 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC to yield *N1*-{4-[4-amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.18 g, 0.34 mmol) as a white solid: ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.89 (dd, 1H), 8.31(d, 1H), 8.26 (s, 1H), 8.00 (t, 1H), 7.88 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 6.09 (d, 1H), 5.93 (d, 1H), 5.76 (m, 1H), 5.31 (m, 1H), 4.74 (m, 1H), 3.94 (s, 3H), 2.84 (m, 1H), 2.02 (m, 1H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5 μ m, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 8.50 min. MS: MH⁺ 529.

10 Example 532: *N*1-{4-[4-Amino-1-(3-hydroxycyclopentyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A mixture of *N*1-{4-[4-amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.10 g, 0.19 mmol) and 10% palladium on carbon (0.03 g) in ethanol (10 mL) was stirred at ambient temperature under one atmosphere of hydrogen overnight. The mixture was filtered and the filtrate was purified by preparative HPLC to yield *N*1-{4-[4-amino-1-(3-hydroxycyclopentyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.07 g, 0.13 mmol) as a white solid: ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.91 (dd, 1H), 8.31(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.17 (m, 1H), 4.97 (m, 1H), 4.22 (m, 1H), 3.94 (s, 3H), 1.79-2.41 (m, 6H); MS: MH⁺ 531.

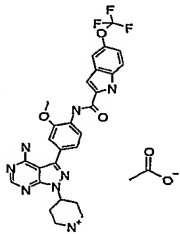
25 Example 533: 4-(4-Amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate

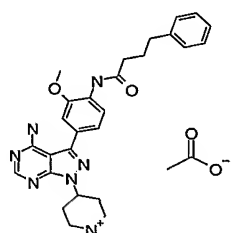
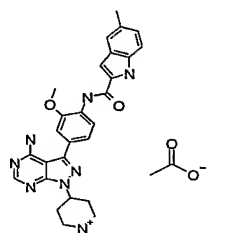
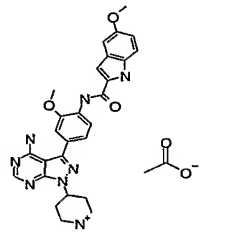
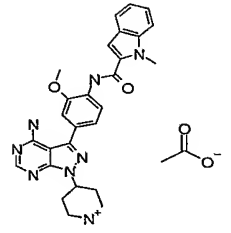
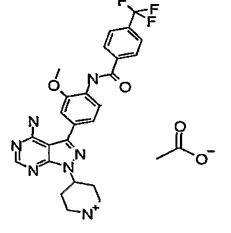
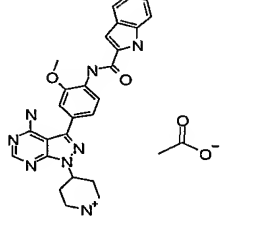
Oxalyl chloride (0.06 mL, 0.60 mmol) was added into a solution of indole-2-carboxylic acid (0.88 g, 0.546 mmol) in dichloromethane (5 mL) and tetrahydrofuran (5 mL) at 0°C. *N,N*-dimethylformamide (3 drops from 0.1 mL syringe) was added and the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. The solvents and excess of reagents were evaporated under reduced pressure. The residue was taken into dichloromethane (2 mL) and the resulting

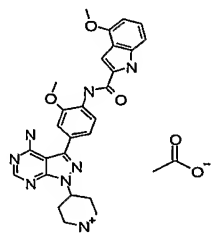
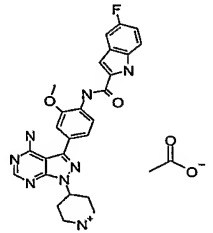
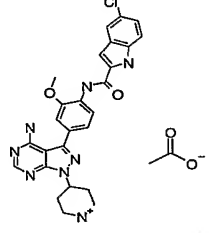
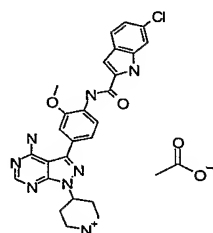
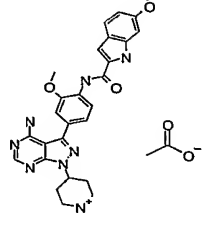
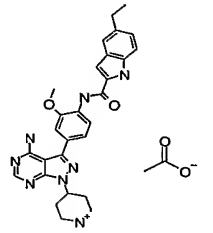
solution (1.25 mL) was added into a solution of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.12 g, 0.27 mmol) and pyridine (0.4 mL) in dichloromethane (1 mL). The mixture was stirred at ambient temperature for 2 hours. Trifluoroacetic acid (1 mL) was added and the mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-(4-amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate (0.07 g, 0.14 mmol) as a white solid: ¹H NMR (DMSO-*d*₆, 400MHz) δ 11.85 (br, 1H), 9.45 (s, 1H), 8.24 (d, 1H), 8.12 (d, 1H), 7.68(d, 1H), 7.48 (d, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.30 (d, 1H), 7.24 (t, 1H), 7.09 (t, 1H), 4.77 (m, 1H), 3.97 (s, 3H), 3.11 (m, 2H), 2.68 (m, 2H), 2.09 (m, 2H), 1.89 (s, 3H), 1.84 (m, 2H); MS: MH⁺ 483.

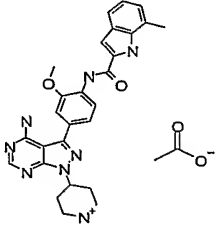
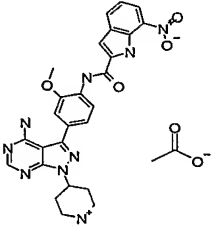
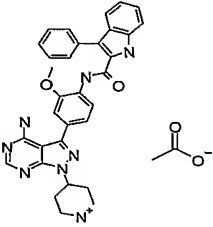
Example 534-549:

Used the same protocol that was used to prepare 4-(4-amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate (Example 533), the following compounds were made.

Structure	MS: MH ⁺	HPLC Rt (min) (Hypersil C18, 5 μ m, 100A, 250x4.6mm; 25 % - 100 % acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	567	6.97	534

	486	5.89	535
	497	6.28	536
	513	5.61	537
	497	6.39	538
	512	6.22	539
	483	5.73	540

	513	7.78	541
	501	8.23	542
	517	8.7	543
	517	8.73	544
	513	7.83	545
	511	9.07	546

	497	8.37	547
	528	7.9	548
	559	9.5	549

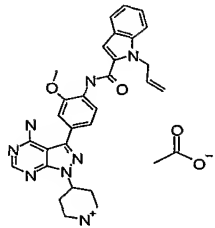
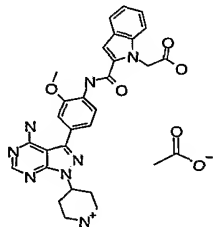
Example 550: 4-[4-Amino-3-(4-[[[(1-ethyl-1*H*-2-indolyl)carbonyl]amino}-3-methoxyphenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate

Sodium hydride, 60% suspension in mineral oil (0.006 g, 0.15 mmol) was added into the solution of *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1*H*-2-indolecarboxamide (0.08 g, 0.14 mmol) in *N,N*-dimethylformamide (1.0 mL) at 0°C. The mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. A solution of ethyl iodide (0.02 g, 0.14 mmol) in *N,N*-dimethylformamide (0.5 mL) was added in and the mixture was stirred at ambient temperature overnight. Ethyl iodide (0.01 g, 0.07 mmol) was added in and the mixture was stirred at ambient temperature overnight. Trifluoroacetic acid (3 mL) was added and the mixture was stirred at ambient temperature for 24 hours. The solvents and excess reagents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-[4-amino-3-(4-[[[(1-ethyl-1*H*-2-indolyl)carbonyl]amino]-3-methoxyphenyl)-1*H*-

pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (0.05 g, 0.09 mmol) as a white solid: ^1H NMR (DMSO-*d*₆, 400MHz) δ 9.43 (s, 1H), 8.27 (s, 1H), 8.14 (d, 1H), 7.71(d, 1H), 7.61 (d, 1H), 7.34 (s, 2H), 7.31 (t, 2H), 7.15 (t, 1H), 4.96 (m, 1H), 4.62 (q, 2H), 3.96 (s, 3H), 3.00 (m, 2H), 2.28 (m, 2H), 2.03 (m, 2H), 1.91 (s, 3H), 1.33 (t, 3H); MS: MH⁺ 511.

Example 551 and 552:

Used the same protocol that was used to prepare 4-[4-amino-3-(4-{[(1-ethyl-1*H*-2-indolyl)carbonyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (Example 550), the following compounds were made.

Structure	MS: MH ⁺	HPLC Rt (min) (Hypersil C18, 5 μ m, 100A, 250x4.6mm; 25% - 100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	523	9.12	551
	540	6.03	552

Example 553: 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A solution of racemic 3-iodo-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-

d]pyrimidin-4-amine (0.050 g, 0.00014 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.033 g, 0.00015 mol), sodium carbonate (0.037 g, 0.00037 mol) and tetrakis (triphenylphosphine) palladium (0) (0.016 g, 0.000014 mol) at 80° C for 18 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.040 g, 0.00009 mol).

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.10- 7.22 (m, 5H), 4.74-4.84 (m, 1H), 2.94 (dd, 1H), 2.79 (d, 1H), 2.36 (t, 1H), 2.22 (s, 3H), 1.89 (s, 3H), 1.86-2.01 (m, 3H), 1.76-1.84 (m, 1H), 1.60-1.75 (m, 1H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.74 min.; MS: MH⁺ 401.

Example 554: 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate BSF 4058532F.

A solution of racemic 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.050 g, 0.00012 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.029 g, 0.00014 mol), sodium carbonate (0.033 g, 0.00031 mol) and tetrakis(triphenylphosphine) palladium (0) (0.014 g, 0.00001 mol) at 80° C for 20 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.038 g, 0.00007 mol).

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.09- 7.22 (m, 5H), 4.71-4.82 (m, 1H), 3.44 (t, 2H), 3.21 (s, 3H), 3.04 (dd, 1H), 2.91 (d, 1H), 2.47-2.60 (m, 3H), 1.94-2.09 (m, 3H), 1.89 (s, 3H), 1.75-1.84 (m, 1H), 1.57-1.74 (m,

1H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.26 min.; MS: MH⁺ 445.

- 5 Example 555: *Trans* 1-{4-[4-amino-3-(3-chloro-4-{[4-(trifluoromethyl)benzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}-4-methylhexahydropyrazinedium dimaleate

A. *Tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate

- 10 A solution of 4-bromo-2-chloroaniline (5.00 g, 0.0242 mol) in tetrahydrofuran (50 mL) was reacted with a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (53.2 mL, 0.0532 mol). The mixture was stirred 15 minutes at ambient temperature. Di-*tert*-butyl dicarbonate (6.34 g, 0.0290 mol) was added and the solution was stirred for 2 hours. The solvent was removed *in vacuo*, and the crude material was purified by flash column chromatography on silica
15 using heptane /ethyl acetate (4:1). The solvent was removed *in vacuo* to give *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate as a white solid (4.214 g, 0.0137 mol).
¹H NMR (DMSO-*d*₆, 400MHz) δ 8.75 (s, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 7.50 (dd, 1H), 1.46 (s, 9H);
20 TLC (heptane/ethylacetate 4:1) R_f 0.54.

B. *Tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

- A mixture of *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate (2.10 g, 0.00685 mol), diboron pinacol ester (2.09 g, 0.00822 mol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.17 g, 0.00021 mol) and potassium acetate (2.02 g, 0.02055 mol) in *N,N*-dimethylformamide (50 ml) was heated at 80°C under a nitrogen atmosphere for 6 hours. The solvent was removed *in vacuo*. The residue was
30 triturated with heptane (70 mL) and the resulting solids were removed by filtration through a pad of Celite ® 521. The heptane was removed *in vacuo* to give *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate as a

grey solid (1.93 g, 0.00546 mol): ^1H NMR (DMSO- d_6 , 400MHz) δ 8.65 (s, 1H), 7.74 (d, 1H), 7.61 (d, 1H), 7.56 (dd, 1H), 1.47 (s, 9H), 1.29 (s, 12H).

- 5 C. *Trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate

A mixture of *trans* 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.20 g, 0.00498 mol), *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.93 g, 0.00548 mol), sodium carbonate (1.32 g, 0.01245 mol) in 1,2-dimethoxyethane (50 mL) and water (100 mL) was stirred rapidly and tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred 6 hours at 80°C, after which time additional tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred an additional 16 hours at 15 80°C. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate (200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The product was purified by flash column 20 chromatography on silica using dichloromethane/methanol/ammonium hydroxide (90:10:0.5). The solvent was removed *in vacuo* to give *trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate as a white solid (1.993 g, 0.00368 mol):
 ^1H NMR (DMSO- d_6 , 400MHz) δ 8.76 (s, 1H), 8.23 (s, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.57 (dd, 1H), 4.58-4.71 (m, 1H), 2.15 (s, 3H), 1.89-2.61 (m, 15H), 1.49 (s, 9H), 1.40-1.48 (m, 2H); TLC (dichloromethane/methanol = 90:10) R_f 0.13, MS: M^+ 541.

- 30 D. *Trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
Trans tert-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate (1.993 g, 0.00368 mol)

was added to a solution of 20% trifluoroacetic acid in dichloromethane. The mixture was stirred for 2 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL) and washed with a 1.0 M aqueous solution of sodium hydroxide (2 x 25 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give *trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.564 g, 0.00355 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.20 (s, 1H), 7.45 (d, 1H), 7.31 (dd, 1H), 6.92 (d, 1H), 4.57-4.63 (m, 1H), 2.23-2.55 (m, 9H), 2.14 (s, 3H), 1.89-2.08 (m, 6H), 1.38-1.52 (m, 2H); TLC (dichloromethane/methanol = 90:10) R_f 0.08; MS: MH⁺ 441.

E. *Trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethyl)benzamide dimaleate

To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethyl)-1-benzenecarbonyl chloride (0.188 g, 0.00090 mol) was added dropwise, keeping the temperature below -5° C. The mixture was stirred at -10° C for 15 minutes, and then at ambient temperature for 18 hours. After addition of an 1N aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the purified free base (0.032 g, 0.000052 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to reflux. After addition of a solution of maleic acid (0.018 g, 0.000156mol) in absolute ethanol (1 mL) the solution was refluxed for further 15 minutes. The mixture was cooled to ambient

temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethyl)benzamide dimaleate as a white solid (0.020 g, 0.00002 mol): ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.42 (s, 1H), 8.26 (s, 1H), 8.20 (d, 2H), 7.96 (d, 2H), 7.80-7.83 (m, 2H), 7.46 (dd, 1H), 6.80-7.20 (b, 2H), 6.13 (s, 4H), 4.61-4.73 (m, 1H), 2.52-2.64 (m, 4H), 2.23-2.46 (m, 5H), 2.16 (s, 3H), 1.90-2.10 (m, 6H), 1.42-1.56 (m, 2H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.97 min.; MS: MH⁺ 613.

Example 556: *Trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate

To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethoxy)-1-benzenecarbonyl chloride (0.203 g, 0.00091 mol) was added dropwise, keeping the temperature less than -5° C. The mixture was stirred at -10° C for 15 minutes and then at ambient temperature for 18 hours. After addition of an 1N aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the purified free base (0.034 g, 0.000054 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to reflux. A solution of maleic acid (0.019 g, 0.000162 mol) in absolute ethanol (1 mL) was added and the solution was refluxed for 15 minutes. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal

amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* N1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate as a white solid (0.020 g, 0.00002 mol): ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.29 (s, 1H), 8.26 (s, 1H), 8.14 (d, 2H), 7.78-7.87 (m, 2H), 7.68 (dd, 1H), 7.57 (d, 2H), 6.80-7.20 (b, 2H), 6.11 (s, 4H), 4.65-4.77 (m, 1H), 2.38-3.60 (m, 12H), 1.95-2.15 (m, 6H), 1.51-1.68 (m, 2H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.41 min.; MS: MH⁺ 629.

10 Example 557: *Trans* 3-(3-chloro-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amineacetate

A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 5-methyl-2-furfural (0.052 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxymethylborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional two equivalents of sodium triacetoxymethylborohydride (0.672 g, 0.00318 mol) were added in two 24 hour intervals. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *trans* 3-(3-chloro-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.129 g, 0.00022 mol): ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.20 (s, 1H), 7.51 (d, 1H), 7.39 (dd, 1H), 6.93 (d, 1H), 6.20 (d, 1H), 6.14 (t, 1H), 5.98 (d, 1H), 4.55-4.66 (m, 1H), 4.38 (d, 2H), 2.23 (s, 3H), 2.18-2.61 (m, 10 H), 2.14 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 5H), 1.37-1.53 (m, 2H); RP-HPLC (Delta Pak C18,

5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.48 min.;MS: MH⁺ 535.

Example 558: *Trans* 3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 2-chloro-6-fluorobenzaldehyde (0.076 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxymethylborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional three equivalents of sodium triacetoxymethylborohydride (1.008 g, 0.00477 mol) were added in three 24 hour intervals, after which time all the starting material had been consumed. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give to give *trans* 3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.074 g, 0.00011 mol): ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.20 (s, 1H), 7.52 (d, 1H), 7.35-7.47 (m, 4H), 6.99 (d, 1H), 5.75 (t, 1H), 4.55-4.66 (m, 1H), 4.57 (d, 2H), 2.25-2.61 (m, 11 H), 2.16 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 4H), 1.37-1.53 (m, 2H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.97 min.;MS: MH⁺ 583.

Example 559: *Trans* N1-(4-{4-amino-1-[1-(1*H*-2-imidazolylcarbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-

phenyl-1-cyclopropanecarboxamide maleate

A mixture of *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00041 mol) in toluene (10 mL) was reacted with 5*H*,10*H*-diimidazo[1,5-*a*:1,5-*d*]pyrazine-5,10-dione (0.040 g, 0.00021 mol) at reflux for 18 hours. An additional equivalent of 5*H*,10*H*-diimidazo[1,5-*a*:1,5-*d*]pyrazine-5,10-dione was added and the mixture was refluxed an additional 6 hours. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the free base (0.103 g, 0.00017 mol). The free base was dissolved in absolute ethanol (10 mL) and heated to reflux. After addition of a solution of maleic acid (0.030 g, 0.00034 mol) in absolute ethanol (1 mL) the solution was refluxed for 15 minutes, after which time a precipitate formed. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans* *N*1-(4-{4-amino-1-[1-(1*H*-2-imidazolylcarbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide maleate as a white solid (0.055 g, 0.00008 mol):

¹H NMR (DMSO-*d*₆, 400MHz) δ 9.63 (s, 1H), 8.26 (s, 1H), 8.22 (d, 1H), 8.00 (b, 1H), 7.74 (b, 1H), 7.43-7.48 (m, 1H), 7.16-7.33(m, 7H), 6.21 (s, 2H), 4.97-5.13 (m, 1H), 2.91-3.47 (m, 4H), 2.53-2.65 (m, 1H), 2.30-2.45 (m, 1H), 2.07-2.26 (m, 2H), 1.95-2.07 (m, 2H), 1.45-1.50 (m, 1H), 1.28-1.32 (m, 1H); RP-HPLC (Delta Pak C18, 5μm, 300Å, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.17 min.; MS: MH⁺ 578.

Example 560: *Cis* *N*1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide acetate

A. *Cis* *N*1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide

A mixture of *cis* N1-{4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenylcyclopropane-1-carboxamide (0.605 g, 0.0012 mol), lithium perchlorate (0.189 g, 0.0018 mol) and potassium cyanide (0.116 g, 0.0018 mol) in acetonitrile (60 ml) was heated at 80°C for two days. Cooled to ambient temperature, diluted with water (30 mL) and extracted with diethyl ether (3x 30 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica using dichloromethane/methanol (95:5). The solvent was removed *in vacuo* to give *cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenyl-1-cyclopropanecarboxamide as a white solid (0.602 g, 0.0011 mol): ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.64 (s, 1H), 8.23 (t, 2H), 7.31 (t, 2H), 7.25 (s, 1H), 7.17- (m, 4H), 4.61-4.62 (m, 1H), 3.91 (s, 1H), 2.66 (s, 2H), 2.55-2.62 (m, 1H), 2.31-2.45 (m, 3H), 1.58-1.89 (m, 6H), 1.45-1.53 (m, 1H), 1.28-1.38 (m, 1H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.21 min.; MS: MH⁺ 538.

B. *Cis* N1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate

To a solution of *cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenyl-1-cyclopropane-carboxamide (0.200 g, 0.00037 mol) in methanol (20 ml) and ammonium hydroxide (1 mL) Raney nickel (0.5 mL) was added. The mixture was stirred 18 hours under a hydrogen atmosphere (1 atm). The reaction mixture was filtered through celite and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8 μ m, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *Cis* N1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenyl-1-

cyclopropanecarboxamide acetate as a white solid (0.045 g, 0.000083 mol).: ^1H NMR (DMSO- d_6 , 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.65-4.67 (m, 1H), 3.91 (s, 3H), 2.84-2.91 (m, 1H), 2.53-2.55 (m, 1H), 2.33-2.40 (m, 4H), 1.85 (s, 3H), 1.35-1.80 (m, 9H), 1.30-1.33 (m, 1H); RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.29 min.; MS: MH^+ 444

Example 561: *Cis* N1-(4-{4-amino-1-[4-(2-amino-2-oxoethyl)-4-

hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-

10 methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide

To a well-stirred solution of *cis* N1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00037 mol) in dimethylsulfoxide (4 mL) potassium carbonate (0.216 g, 0.00156 mol) was added at ambient

15 temperature. A 30% aqueous solution of hydrogen peroxide (0.6 mL) was added dropwise, keeping the temperature constant. The mixture was stirred at ambient temperature for 32 hours. Water (20 mL) was added to the mixture, and the precipitate which formed was filtered. The precipitate was washed with water and dried *in vacuo*. The solid was purified by preparative RP-HPLC (Rainin C18, 8 μm , 20 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *cis* N1-(4-{4-amino-1-[4-(2-amino-2-oxoethyl)-4-hydroxycyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(trans)-2-phenyl-1-cyclopropanecarboxamide as a white solid 25 (0.117 g, 0.00021 mol): ^1H NMR (DMSO- d_6 , 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22 (s, 1H), 7.43-7.48 (m, 1H), 7.15-7.35 (m, 7H), 7.05-7.10 (m, 1H), 4.97 (s, 1H), 4.61-4.71 (m, 1H), 3.91 (s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.24 (s, 2H), 1.55-1.81 (m, 6H), 1.45-1.53 (m, 1H), 1.28-1.36 (m, 1H); RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 30 20 min, 1mL/min) R_t 14.05 min.; MS: MH^+ 556.

Example 562: *Cis* N1-[4-(4-amino-1-{4-[(dimethylamino)methyl]-4-

hydroxycyclohexyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate

To a solution of *cis* *N*1-{4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenylcyclopropane-1-carboxamide (0.190 g, 0.000302 mol) in 2-propanol (10 mL) a 2 M solution of dimethylamine in methanol (0.91 mL) was added and the resulting mixture was heated at 65° C in a pressure tube for 18 hours. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 Å, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 mL/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give *Cis* *N*1-[4-(4-amino-1-{4-[(dimethylamino)methyl]-4-hydroxycyclohexyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate as a white solid (0.109 g, 0.000177 mol).:

¹H NMR (DMSO-*d*₆, 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.56-4.68 (m, 1H), 3.91 (s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.28 (s, 6H), 2.24 (s, 2H), 1.91 (s, 3H), 1.63-1.78 (m, 4H), 1.44-1.58 (m, 3H), 1.28-1.36 (m, 1H); RP-HPLC (Delta Pak C18, 5µm, 300Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.54 min.; MS: MH⁺ 556.

Example 563: *Trans* *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolicarboxamide acetate

A solution of *trans* 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00046 mol) in *N,N*-dimethylformamide (10 mL) was reacted with 1-hydroxy-7-azabenzotriazole (0.068 g, 0.00050 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.132 g, 0.00069 mol), D-Boc-proline (0.108 g, 0.00050 mol) and *N,N*-diisopropylethylamine (0.184 g, 0.00142 mol) at ambient temperature for 24 hours. The solvent was removed *in vacuo* and the residue was

partitioned between dichloromethane (10 mL) and a 5% aqueous citric acid solution (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (15 mL) and dried over magnesium sulfate.

- 5 The solvent was removed *in vacuo* and the residue was stirred in 20% trifluoroacetic acid in dichloromethane for 6 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 Å, 25 cm; 5% isocratic for five minutes, then 5%-40% acetonitrile - 0.1M ammonium acetate over 20 min, 21 ml/min). The acetonitrile was removed *in*
10 *vacuo* and the aqueous mixture was lyophilized to give *trans* N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolecarboxamide acetate (0.096 g, 0.00016 mol) as a white solid.

- ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.33 (s, 1H), 8.45 (d, 1H), 8.22 (s, 1H), 7.25 (s,
15 1H), 7.21 (d, 1H), 4.58-4.69 (m, 1H), 3.93 (s, 3H), 3.77 (dd, 1H), 2.96-3.04 (m, 1H), 2.74-2.84 (m, 1H), 2.47-2.58 (m, 5H), 2.23-2.45 (m, 5H), 2.14 (s, 3H), 1.91 (s, 3H), 1.88-2.11 (m, 7H), 1.78-1.88 (m, 1H), 1.60-1.69 (m, 2H), 1.39-1.54 (m, 2H); RP-HPLC (Delta Pak C18, 5 μ m, 300Å, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R_t 8.47 min.; MS: MH⁺ 534.

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Example 564: 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate

A. 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate

- 25 A solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 0.019 mol) in *N,N*-dimethylformamide (50 mL) was reacted with 60% sodium hydride in oil (0.92 g, 0.023 mol) at ambient temperature. The mixture was stirred for 15 minutes, and 4-nitropyridine-*N*-oxide (5.37 g, 0.038 mol) was added. The mixture was heated at 100° C. for 18 hours. The precipitate which formed was filtered,
30 washing with *N,N*-dimethylformamide and ethyl acetate to give 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (3.79 g, 0.011 mol) as a tan solid:

^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ 8.38 (s, 1H), 8.34 (d, 2H), 8.24 (d, 2H); RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 7.36 min.; MS: MH^+ 355.

5 B. 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate

A suspension of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (0.140 g, 0.00040 mol) in dimethoxyethane (7 mL) and water (15 mL) was reacted with 4-phenoxyphenylboronic acid (0.093 g, 0.00043 mol), sodium
10 carbonate (0.105 g, 0.00099 mol) and tetrakis(triphenylphosphine) palladium (0) (0.046 g, 0.00004 mol) at 80° C for 18 hours. The solid was filtered to give 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.138 g, 0.00035 mol) as a brown solid. A portion (0.040 g, 0.00010 mol) was purified by preparative RP-HPLC (Rainin C18, 8 μm , 300 A, 25 cm; 40% isocratic
15 for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyophilized to give the product 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate as a white solid (0.013 g, 0.00003 mol). ^1H NMR ($\text{DMSO}-d_6$,
20 400MHz) δ 8.44 (s, 1H), 8.34-8.41 (m, 4H), 7.77 (d, 2H), 7.45 (t, 2H), 7.13-7.24 (m, 5H);
RP-HPLC (Delta Pak C18, 5 μm , 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.66 min.; MS: MH^+ 397.

25 Example 565: 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.100 g, 0.00025 mol) and 10% palladium on carbon (0.016 g, 0.00002 mol) in acetic acid (3 mL) was reacted with sodium
30 hypophosphite monohydrate (0.033 g, 0.00038 mol) at 60° C. After 2 hours, an additional 10% palladium on carbon (0.016 g, 0.00002 mol) was added. The mixture was stirred 18 hours after which time additional 10% palladium on carbon (0.016 g,

0.00002 mol) and sodium hypophosphite monohydrate (0.033 g, 0.00038 mol) was added. The mixture was stirred for an additional 24 hours. The mixture was filtered through Celite ® 521, washing with acetic acid. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25
5 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyophilized to give 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.020 g, 0.00005 mol) as a white solid:

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.71 (d, 2H), 8.46 (s, 1H), 8.39 (dd, 2H), 7.78 (d,
10 2H), 7.46 (t, 2H), 7.13-7.25 (m, 5H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) *R*_t 17.31 min.; MS: MH⁺ 381.

Example 566: *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-
15 methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A. *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-
methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A suspension of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-
pyridiniumolate (0.500 g, 0.0014 mol) in dimethoxyethane (15 mL) and water (30
20 mL) was reacted with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.631 g, 0.00155 mol), sodium
carbonate (0.374 g, 0.0035 mol) and tetrakis(triphenylphosphine) palladium (0)
(0.163 g, 0.00014 mol) at 80° C for 18 hours. The solid was filtered and washed with
water. The solid was slurried in ethyl acetate for 18 hours and filtered, washing with
25 ethyl acetate. The solid was dried *in vacuo* to give crude 4-[4-amino-3-(3-methoxy-
4-[(1-methyl-1*H*-2-indolyl)-carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-
yl]-1-pyridiniumolate (0.523 g, 0.0010 mol) as a brown solid:

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M
ammonium acetate over 10 min, 1mL/min) *R*_t 10.92 min.;

30 MS: MH⁺ 507.

B. *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-

methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A suspension of 4-[4-amino-3-(3-methoxy-4-{[(1-methyl-1*H*-2-indolyl)carbonyl]amino} phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.200 g, 0.00039 mol) and 10% palladium on carbon (0.042 g, 0.00004 mol) in acetic acid (3 mL) was reacted with sodium hypophosphite monohydrate (0.063 g, 0.00059 mol) at 60° C for 2 hours. Additional 10% palladium on carbon (0.042 g, 0.00004 mol) and sodium hypophosphite (0.045 g, 0.00042 mol) was added and the mixture was stirred for 24 hours. The solvent was removed *in vacuo* and the residue was slurried in methanol for 4 hours. The mixture was filtered through Celite ® 521, washing with methanol. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25 cm; 50% isocratic for five minutes, then 50%-100% acetonitrile - 0.1M ammonium acetate over 25 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.020 g, 0.00004 mol) as a white solid: ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.48 (s, 1H) 8.72 (d, 2H), 8.47 (s, 1H), 8.42 (d, 2H), 8.20 (d, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.48 (s, 1H), 7.42 (d, 1H), 7.36 (s, 1H) 7.34 (t, 1H), 7.16 (t, 1H), 4.05 (s, 3H), 3.99 (s, 1H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile - 0.1M ammonium acetate over 20 min, 1mL/min) R_t 19.50 min.; MS: MH⁺ 491.

Examples 567: 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine; and

Example 568: 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A solution of 3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00079 mol) in *N*-methyl pyrrolidinone (10 mL) was reacted with 60% sodium hydride in oil (0.032 g, 0.00079 mol). After gas evolution ceased, the mixture was stirred at ambient temperature for 30 minutes, and 5-bromo-2-nitropyridine (0.161 g, 0.00079 mol) was added and heated at 40° C for 18 hours. Additional 60% sodium hydride in oil (0.032 g, 0.00079 mol) was added and the mixture was stirred an additional 2 hours. The solvent was removed *in vacuo* and the

residue was partitioned between dichloromethane (15 mL) and water (25 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica using heptane/ethyl acetate (1:2) as an eluent to give two products. The less polar compound, 1-(6-nitro-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.007 g, 0.00002 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.53 (d, 1H) 8.31 (s, 1H), 7.97 (dd, 1H), 7.73 (d, 2H), 7.44 (t, 2H), 7.12-23 (m, 5H), 6.60 (d, 1H), 6.20 (s, 2H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.38 min.; MS: MH⁺ 396.

The more polar compound, 3-(4-phenoxyphenyl)-1-(5-bromo-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.030 g, 0.00007 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.60-8.64 (m, 1H) 8.37 (s, 1H), 8.20 (d, 1H), 8.03-8.08 (m, 1H), 7.76 (d, 2H), 7.41-7.49 (m, 3H), 7.12-7.23 (m, 5H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 16.32 min.; MS: MH⁺ 381.

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A general procedure for reductive amination using *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as

starting material and an aldehyde is described in Example 569. Various other aldehydes can be substituted for 2-methoxy-3-formyl-pyridine of Example 569 to attach other Z¹⁰⁰ groups.

- 5 Examples 569: *trans*-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methyl-piperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate; and

 A mixture of *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 eq.), 2-
10 methoxy-3-formyl-pyridine (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile –
15 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products. The following two compounds were prepared according to the procedure above:
trans-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methyl-piperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate
¹H NMR (DMSO-*d*₆, 400MHz) δ 8.18 (s, 1H), 8.06 (dd, 1H), 7.61 (d, 1H), 7.35 (d, 2H), 6.95 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.60 (m, 1H), 4.26 (d, 2H), 3.94 (s, 3H),
20 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.07 min.
MS: MH⁺ 528.

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Example 570: *trans*-3-{4-[(1*H*-2-indolylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

Trans-3-{4-[(1*H*-2-indolylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)-
30 cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate was prepared as in the method of Example 569 except that 2-formyl-indole was used instead of 2-methoxy-3-formyl-pyridine.

¹H NMR (DMSO-*d*₆, 400MHz) δ 11.08 (s, 1H), 8.19 (s, 1H), 7.44 (d, 1H), 7.36 (d, 2H), 7.32 (d, 1H), 7.01 (t, 1H), 6.95 (t, 1H), 6.81 (d, 2H), 6.47 (t, 1H), 6.35 (s, 1H), 4.60 (m, 1H), 4.45 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
5 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.74 min.
MS: MH⁺ 536.

- 10 Example 571: *Trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate
- Trans*-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.105
15 g, 0.000199mol) was dissolved in 30% hydrogen bromide in acetic acid (4 mL) and the mixture was refluxed for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-
20 yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate (0.0204 g, 0.0000324 mol) as a white solid.
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.18 (s, 1H), 7.29 (m, 4H), 6.68 (d, 2H), 6.40 (t, 1H), 6.15 (m, 1H), 4.60 (m, 1H), 4.09 (d, 2H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);
25 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 9.40 min. MS: MH⁺ 514.

A general procedure for reductive amination with *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-
30 *d*]pyrimidin-4-amine and an aldehyde as starting material is described in Example 572:

Example 572: *Trans*-5-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyanilino)methyl]-4-chloro-1,3-thiazol-2-amine diacetate

5 A mixture of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 eq.), 2-amino-4-chloro-5-formyl-1,3-thiazole (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched
10 with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired product.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.19 (s, 2H), 7.06 (m, 3H), 6.68 (d, 1H),
15 5.76 (t, 1H), 4.60 (m, 1H), 4.30 (d, 2H), 3.85 (s, 3H), 2.6-2.2 (br, 9H), 2.17 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.59 min.

MS: MH⁺ 583.

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Examples 573 and 574 were prepared according to the method of Example 572:

Example 573: *Trans*-3-(3-methoxy-4-[(5-methyl-3-isoxazolyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-
25 amine acetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.04 (m, 2H), 6.68 (d, 1H), 6.16 (s, 1H),
5.86 (t, 1H), 4.60 (m, 1H), 4.37 (d, 2H), 3.86 (s, 3H), 2.6-2.2 (br, 9H), 2.40 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium
30 acetate over 20 min, 1mL/min) R_t 11.53 min.

MS: MH⁺ 532.

Example 574: *Trans*-3-{3-methoxy-4-[(1,3-thiazol-4-ylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 9.08 (s, 1H), 8.19 (s, 1H), 7.47 (s, 1H), 7.06 (s, 1H),
5 7.03 (d, 1H), 6.68 (d, 1H), 5.76 (t, 1H), 4.60 (m, 1H), 4.52 (d, 2H), 3.88 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.17 min.

MS: MH⁺ 534.

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A general procedure for the synthesis of benzotetrahydrofuran-derivatives with *trans*- 3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and a 2-hydroxybenzaldehyde as starting materials is given in Example 575.

15

Example 575: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

Trans-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-
20 pyrazolo[3,4-*d*]pyrimidin-4-amine (1 equiv., 0.0001–0.0002 mol scale) and 2-hydroxy-4,6-dichlorobenzaldehyde (1 equiv.) were combined in absolute ethanol (5 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue dried overnight to yield the corresponding imine, which was used without further purification.

25 Trimethylsulfoxonium iodide (2.5 equiv.) was dissolved in anhydrous dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in parafine (2.5 equiv.) was added at once. After 10 min., the solution of the imine in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution
30 was poured into ice-cold water (50 mL) and extracted with dichloromethane (2x40 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25

min, 21mL/min) to yield the final compound.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.39 (d, 2H), 7.14 (s, 1H), 7.07 (s, 1H), 6.80 (d, 2H), 6.56 (d, 1H), 5.34 (m, 1H), 4.80 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

- 5 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 16.03 min.

MS: MH⁺ 593.

- 10 Example 576: *Trans*-3-{4-[(4-chloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

- Trans*-3-{4-[(4-chloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate was prepared using the method of Example 575 except 2-hydroxy-4,6-dichlorobenzaldehyde was replaced with 2-hydroxy-4-chlorobenzaldehyde.

- 15 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.20 (s, 1H), 7.39 (d, 2H), 7.28 (t, 1H), 6.99 (d, 1H), 6.89 (d, 1H), 6.81 (d, 2H), 6.53 (d, 1H), 5.34 (m, 1H), 4.74 (dd, 1H), 4.60 (m, 1H), 4.38 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- 20 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.42 min.
- MS: MH⁺ 559.

- 25 Example 577: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
- Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate was prepared using the method of Example 575 except
- 30 *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine was used instead of *trans*-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.20 (s, 1H), 7.11 (m, 4H), 6.80 (d, 1H), 5.45(m, 2H), 4.84 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 3.82 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

5 ammonium acetate over 20 min, 1mL/min) R_t 16.85 min.

MS: MH⁺ 623.

Intermediate 5: *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

10

A. *Tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

A mixture of benzyl *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (9.54 g, 0.027 mol), *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (10.0 g, 0.0225 mol),
15 tetrakis-(triphenylphosphine)palladium (1.56 g, 0.00135 mol) and sodium carbonate (5.97 g, 0.0563 mol) was heated in a mixture of ethylene glycol dimethyl ether (120 mL) and water (60 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed
20 under the reduced pressure. The residue was partitioned between water (150 mL) and dichloromethane (150 mL); the organic phase was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was triturated in diethyl ether and the precipitate was collected by filtration and dried to
25 yield *tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (10.1 g, 0.0186 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.00 (s, 1H), 8.23 (s, 1H), 7.64 (d, 2H), 7.43 (d, 2H), 7.36 (m, 5H), 5.18 (s, 2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H);

30 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 18.58 min.

B. *Tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

To a solution of *tert*-butyl 4-[4-amino-3-(4-
[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-
5 piperidinecarboxylate (5.0 g, 0.0092 mol) in tetrahydrofuran (150 mL) 10%
palladium on carbon (1.0 g) was added and the reaction mixture was hydrogenated
on a Parr shaker over 96 hours. The catalyst was removed by filtration through a
Celite pad and the filtrate was concentrated under reduced pressure. The residue was
trituated in *n*-heptane and the precipitate was collected by filtration and dried to
10 yield *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-
piperidinecarboxylate (2.51 g, 0.0061 mol) as an off-white solid.
¹H NMR (DMSO-*d*₆, 400MHz) δ 8.20 (s, 1H), 7.35 (d, 2H), 6.69 (d, 2H), 5.42 (s,
2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H);
RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M
15 ammonium acetate over 20 min, 1mL/min) R_t 14.18 min.

Example 578-590:

A general procedure for reductive amination followed by BOC deprotection
that was used to prepare Examples 578-590 is given below:

20

Protocol:

A mixture of *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-1-yl]-1-piperidinecarboxylate (Intermediate 5) (1 eq.), an aldehyde (1.2
eq.), sodium triacetoxymethylborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in
25 anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated
under reduced pressure, trituated in ethyl acetate and treated with with a 4N
aqueous solution of hydrochloric acid. The resulting mixture was stirred for 1 hour;
aqueous phase was neutralized with saturated solution of sodium bicarbonate in
water and the layers separated. Organic phase was concentrated under reduced
30 pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25
cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield
the desired products.

The following compounds were made using the above procedure:

Example 578: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

5 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.57 (d, 1H), 7.53 (d, 1H), 7.39 (d, 2H), 7.23 (m, 2H), 6.85 (d, 2H), 6.80 (s, 1H), 6.66 (t, 1H), 4.70 (m, 1H), 4.51 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.37 min.

10 MS: MH⁺ 440.

Example 579: 3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

15 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 8.06 (d, 1H), 7.61 (d, 1H), 7.36 (d, 2H), 6.96 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.27 (d, 2H), 3.94 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.06 min.

MS: MH⁺ 431.

20

Example 580: 3-(4-[(5-methyl-2-thienyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

25 ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.36 (d, 2H), 6.85 (d, 1H), 6.77 (d, 2H), 6.64 (d, 1H), 6.54 (t, 1H), 4.70 (m, 1H), 4.41 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.38 (s, 3H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.85 min.

MS: MH⁺ 420.

30 Example 581: 3-{4-[(2-furylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.59 (s, 1H), 7.36 (d, 2H), 6.77 (d,

2H), 6.46 (t, 1H), 6.39 (d, 1H), 6.34 (d, 1H), 4.70 (m, 1H), 4.31 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.96 min.

5 MS: MH⁺ 390.

Example 582: 3-[4-(benzylamino)phenyl]-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.34 (m, 6H), 7.24 (t, 1H), 6.73 (d, 10 2H), 6.60 (t, 1H), 4.70 (m, 1H), 4.33 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.32 min.

MS: MH⁺ 400.

15

Example 583: 3-{4-[(2-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.35 (d, 2H), 7.24 (m, 2H), 7.01 (d, 1H), 6.90 (t, 1H), 6.70 (d, 2H), 6.41 (t, 1H), 4.70 (m, 1H), 4.28 (d, 2H), 3.85 (s, 3H), 20 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.73 min.

MS: MH⁺ 430.

25 Example 584: 3-{4-[(3-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 6.96 (m, 2H), 6.81 (d, 1H), 6.72 (d, 2H), 6.59 (t, 1H), 4.70 (m, 1H), 4.30 (d, 2H), 3.74 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

30 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.38 min.

MS: MH⁺ 430.

Example 585: 3-{4-[(4-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.35 (m, 4H), 6.90 (d, 2H), 6.72 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.25 (d, 2H), 3.73 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.37 min.

MS: MH⁺ 430.

10

Example 586: 1-(4-piperidyl)-3-(4-[3-(trifluoromethyl)benzyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.71 (m, 2H), 7.58 (m, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.08 min.

MS: MH⁺ 468.

20 Example 587: 1-(4-piperidyl)-3-(4-[4-(trifluoromethyl)benzyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.70 (d, 2H), 7.60 (d, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

25 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.23 min.

MS: MH⁺ 468.

30 Example 588: 3-(4-[(2-methyl-1,3-thiazol-4-yl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.41 (d, 2H), 7.26 (s, 1H), 6.73 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.36 (d, 2H), 3.07 (m, 2H), 2.70 (s, 3H), 2.65 (m,

2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.13 min.

MS: MH⁺ 421.

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Example 589: 3-{4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.42 (m, 4H), 7.26 (t, 1H), 6.83 (d, 2H), 6.27 (t, 1H), 4.72 (m, 1H), 4.37 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

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RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.32 min.

MS: MH⁺ 452.

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Example 590: 3-(4-[2-fluoro-4-(trifluoromethyl)benzyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.61 (m, 3H), 7.38 (d, 2H), 6.73 (d, 2H), 6.68 (t, 1H), 4.70 (m, 1H), 4.47 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

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RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.83 min.

MS: MH⁺ 486.

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Example 591: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

A mixture of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (g, mol), benzofuran-2-carbaldehyde (0.046 g, 0.000315 mol), sodium triacetoxyborohydride (0.089 g, 0.00042 mol.) and acetic acid (0.024 mL, 0.00042 mol) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, triturated in ethyl acetate (4mL) and treated with a 4N aqueous solution of hydrochloric acid (1 mL). The resulting mixture was stirred for 1 hour; aqueous

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phase was neutralized with saturated solution of sodium bicarbonate in water and the layers separated. The organic phase was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield 3-{4-
5 [(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.027 g, 0.0000457 mol).
¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.55 (m, 2H), 7.22 (m, 2H), 7.06 (m, 2H), 6.80 (d, 1H), 6.75 (s, 1H), 5.80 (t, 1H), 4.70 (m, 1H), 4.57 (d, 2H), 3.89 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
10 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.83 min.
MS: MH⁺ 470.

Example 592: 3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-(4-piperidyl)-
15 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate
Salicylaldehyde (0.063 g, 0.000513 mol) and *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.200 g, 0.000489 mol) were combined in absolute ethanol (5 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced
20 pressure and the residue dried overnight to yield *tert*-butyl 4-[4-amino-3-(4-{[-1-(2-hydroxyphenyl)methylidene]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate which was used without further purification.
Trimethylsulfoxonium iodide (0.269 g, 0.00122 mol) was dissolved in anhydrous dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in paraffine
25 (0.049 g, 0.00122 mol) was added at once. After 10 min., the solution of *tert*-butyl 4-[4-amino-3-(4-{[-1-(2-hydroxyphenyl)methylidene]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water
30 (70 mL) and extracted with dichloromethane (2x50 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure to yield crude *tert*-butyl 4-{4-amino-3-[4-(2,3-dihydrobenzo[*b*]furan-3-

ylamino)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate which was used without further purification. The crude compound was dissolved in ethyl acetate (5 mL) and treated with a 4N aqueous solution of hydrochloric acid (1.5 mL). The resulting emulsion was vigorously stirred for 1 hour; the water layer was

5 neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield 3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-(4-piperidyl)-1H-pyrazolo[3,4-

10 *d*]pyrimidin-4-amine acetate (0.038g, 0.000078 mol) as a white solid

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.19 (s, 1H), 7.41 (m, 3H), 7.25 (t, 1H), 6.89 (m, 4H), 6.51 (t, 1H), 5.35 (m, 1H), 4.79 (m, 2H), 4.27 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M

15 ammonium acetate over 20 min, 1mL/min) R_t 11.38 min.

MS: MH⁺ 428.

Example 593: *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1H-1 λ ⁶-benzo[*d*]isothiazole-

20 1,1-dione acetate

A. 3-chloro-1H-1 λ ⁶-benzo[*d*]isothiazole-1,1-dione

Saccharin (10.0 g, 0.0546 mol) and phosphorus pentachloride (12.6 g, 0.060mol) were heated at 170°C for 1.5 hours. The reaction mixture was cooled to

25 ambient temperature and suspended in diethyl ether (200 mL). The precipitate was collected by filtration, thoroughly washed with diethyl ether and dried to yield 3-chloro-1H-1 λ ⁶-benzo[*d*]isothiazole-1,1-dione (3.7 g, 0.0184 mol) as a white solid which was used without further purification.

MS: MH⁺ 202.

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B. 3-(4-bromoanilino)-1H-1 λ ⁶-benzo[*d*]isothiazole-1,1-dione

To a solution of 3-chloro-1H-1 λ ⁶-benzo[*d*]isothiazole-1,1-dione (1.0 g, 0.00496

mol) in acetone (20 mL), 4-bromoaniline (1.71 g, 0.00992 mol) was added at once and the mixture was stirred for 15 min. The mixture was concentrated under reduced pressure and the residue was suspended in water (100 mL). The precipitate was collected by filtration, thoroughly washed with water and dried to yield 3-(4-bromoanilino)-1*H*-1λ⁶-benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.93 (s, 1H), 8.47 (d, 1H), 8.09 (d, 1H), 7.93 (m, 4H), 7.69 (d, 2H);

10 C. 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ⁶-benzo[*d*] isothiazole-1,1-dione

A mixture of 3-(4-bromoanilino)-1*H*-1λ⁶-benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol), diboron pinacol ester (1.43 g, 0.00561 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.114 g, 0.00014 mol) and potassium acetate (1.37 g, 0.014 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite.

15 The filtrate was concentrated to leave a yellow oil that was triturated in diethyl ether to yield 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ⁶-benzo[*d*] isothiazole-1,1-dione (1.14 g, 0.00297 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.92 (br, 1H), 8.51 (d, 1H), 8.08 (d, 1H), 7.91 (m, 4H), 7.68 (d, 2H), 1.29 (s, 12H).

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D. *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl} anilino)-1*H*-1λ⁶-benzo[*d*]isothiazole-1,1-dione acetate

A mixture of 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ⁶-benzo[*d*] isothiazole-1,1-dione (0.09 g, 0.000234 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.08 g, 0.00018 mol), tetrakis-(triphenylphosphine)palladium (0.013 g, 0.000011 mol) and sodium

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carbonate (0.048 g, 0.00045 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ⁶-benzo[*d*]isothiazole-1,1-dione acetate (0.075 g, 0.000119 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.29 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.79 (m, 2H), 7.66 (d, 2H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.27 min.

MS: MH⁺ 572.

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Example 594: *Cis*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ⁶-benzo[*d*]isothiazole-1,1-dione diacetate

Cis-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ⁶-benzo[*d*]isothiazole-1,1-dione diacetate was prepared from 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ⁶-benzo[*d*]isothiazole-1,1-dione (0.09 g, 0.000234 mol) and *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine by a similar protocol as described above.

¹H NMR (DMSO-*d*₆, 400MHz) δ 8.42 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.84 (m, 2H), 7.62 (d, 2H), 4.80 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.07 (m, 4H), 1.91 (s, 6H), 1.65(m, 2H), 1.58 (m, 2H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.59 min.

MS: MH⁺ 572.

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Example 595: *Trans*-N3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine
acetate

A. *N*1-(4-bromophenyl)-2-fluorobenzamide

5 A solution of 2-fluorobenzoyl chloride (5.82 g, 0.0367 mol) and 4-bromoaniline (6.31 g, 0.0367 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (5.21 g, 0.0407 mol) was added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue partitioned between ethyl acetate (120 mL) and water (100
10 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether (50 mL) and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluorobenzamide (9.6 g, 0.0326 mol) as a white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 10.54 (s, 1H), 7.66 (m, 3H), 7.56 (m, 3H), 7.34 (m,
15 2H). TLC (ethyl acetate / heptane 1:2) R_f 0.37

B. *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide

A mixture of *N*1-(4-bromophenyl)-2-fluorobenzamide (3.3 g, 0.0112 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (2.27 g,
20 0.00561 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica using ethyl acetate/*n*-heptane (1:6) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (3.1 g, 0.010 mol) as a
25 yellow solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 12.13 (s, 1H), 7.93 (d, 2H), 7.62 (m, 3H), 7.51 (m, 1H), 7.31 (m, 2H). TLC (ethyl acetate / heptane 1:4) R_f 0.27

C. *N*1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime

30 A mixture of *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.56 g, 0.00505 mol), hydroxylamine hydrochloride (0.44 g, 0.00631 mol) and sodium bicarbonate (0.53 g, 0.00631 mol) was heated in absolute ethanol (25 mL) at reflux

under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzeneaminoxime (1.21 g, 0.00392 mol) as an off-white solid.

TLC (ethyl acetate / heptane 1:4) R_f 0.12

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D. *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine

To a solution of *N*1-(4-bromophenyl)-2-fluoro-1-benzeneaminoxime (1.51 g, 0.00489 mol) in *N*-methylpyrrolidinone (25 mL), potassium *tert*-butoxide (0.54 g, 0.00513 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ *n*-heptane (1:5) as mobile phase to yield *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine (0.95 g, 0.00329 mol) as a white solid.

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^1H NMR (DMSO- d_6 , 400MHz) δ 9.72 (s, 1H), 8.13 (d, 1H), 7.68 (d, 2H), 7.61 (m, 2H), 7.54 (d, 2H), 7.37 (dd, 1H).

25 TLC (ethyl acetate / heptane 1:4) R_f 0.26

E. *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine (1.30 g, 0.0045 mol), diboron pinacol ester (1.37 g, 0.0054 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.110 g, 0.000135 mol) and potassium acetate (1.32 g, 0.0135 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80°C under an

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- atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was
- 5 purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.40 g, 0.00119 mol) as a white solid.
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.74 (s, 1H), 8.16 (d, 1H), 7.70 (m, 4H), 7.61 (d, 2H), 7.37 (dd, 1H), 1.29 (s, 12H).
- 10 TLC (ethyl acetate / heptane 1:4) R_f 0.21

F. *Trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine acetate

- A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-
- 15 dioxaborolan-2-yl)phenyl]amine (0.10 g, 0.000298 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.101 g, 0.000229 mol), tetrakis-(triphenylphosphine)palladium (0.016 g, 0.0000137 mol) and sodium carbonate (0.061 g, 0.000573 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an
- 20 atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-
- 25 yl}phenyl)benzo[*d*]isoxazol-3-amine acetate (0.102 g, 0.000175 mol) as a white solid.
- ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.81 (s, 1H), 8.23 (s, 1H), 8.19 (d, 1H), 7.88 (d, 2H), 7.65 (m, 4H), 7.40 (m, 1H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
- 30 RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.66 min.
- MS: MH⁺ 524.

Example 596: *Cis-N3*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine diacetate

5 *Cis-N3*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine diacetate was prepared from *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine and *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine by a similar protocol as described above.

10 ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.86 (s, 1H), 8.26 (s, 1H), 8.24 (d, 1H), 7.93 (d, 2H), 7.67 (m, 4H), 7.43 (m, 1H), 4.83 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.08 (m, 4H), 1.91 (s, 6H), 1.74 (m, 2H), 1.62 (m, 2H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.77 min.

15 MS: MH⁺ 524.

Example 597: *N3*-(4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl)benzo[*d*]isoxazol-3-amine acetate

A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.087 g, 0.000258 mol), *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.088 g, 0.000198 mol), tetrakis-(triphenylphosphine)palladium (0.014 g, 0.000012 mol) and sodium carbonate (0.053 g, 0.000495 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure and the residue partitioned between water and dichloromethane. The organic phase was dried with magnesium sulfate and concentrated under reduced pressure to yield crude *tert*-butyl 4-{4-amino-3-[4-(benzo[*d*]isoxazol-3-ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}-1-piperidinecarboxylate which was used without further purification. It was dissolved in ethyl acetate (5 mL) and treated with a 4N aqueous solution of hydrochloric acid (1 mL). The resulting emulsion was vigorously stirred for 1 hour; the water layer

was neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8 μ m, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}benzo[*d*]isoxazol-3-amine acetate (0.009g, 0,0000185 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.82 (s, 1H), 8.20 (m, 2H), 7.89 (d, 2H), 7.65 (m, 4H), 7.41 (t, 1H), 4.74 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H); RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) *R*_t 11.20 min. MS: MH⁺ 427.

Example 598: *Trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A. *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide

*N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.50 g, 0.00485 mol) and a 1M solution of hydrazine in tetrahydrofuran (6.3 mL, 0.0063 mol) were heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. Additional 3 mL of a 1M solution of hydrazine in tetrahydrofuran was added and the stirring at reflux was continued for another 6 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.54 g, 0.0050 mol) as a tan solid.. TLC (ethyl acetate / heptane 1:3) *R*_f 0.10

B. *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine

To a solution of *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.2 g, 0.00391 mol) in *N*-methyl pyrrolidinone (25 mL), potassium *tert*-butoxide (0.50 g, 0.0041 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under

reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.0010 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 12.06 (s, 1H), 9.03 (s, 1H), 7.93 (d, 1H), 7.65 (d, 2H), 7.35 (m, 4H), 7.03 (dd, 1H). TLC (ethyl acetate / heptane 1:3) R_f 0.26

10 C. *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.00101 mol), diboron pinacol ester (0.31 g, 0.00121 mol), [1.1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.025 g, 0.00003 mol) and potassium acetate (0.294 g, 0.003 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:3) as mobile phase to yield *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol) as an off-white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 12.09 (s, 1H), 9.06 (s, 1H), 7.94 (d, 1H), 7.64 (d, 2H), 7.57 (d, 2H), 7.35 (m, 2H), 7.03 (dd, 1H), 1.28 (s, 12H). TLC (ethyl acetate / heptane 1:3) R_f 0.21

D. *Trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.070 g, 0.000159 mol), tetrakis(triphenylphosphine)palladium (0.011 g, 0.0000095 mol) and sodium carbonate (0.042

g, 0.000398 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.035 g, 0.000060 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 12.09 (s, 1H), 9.14 (s, 1H), 8.21 (s, 1H), 7.99 (d, 1H), 7.83 (d, 2H), 7.55 (d, 2H), 7.37 (m, 2H), 7.06 (t, 1H), 4.64 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.49 (m, 2H); RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.96 min. MS: MH⁺ 523.

Example 599: *Trans*-*N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate

A. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide

A solution of 2-fluoro-4-(trifluoromethyl)benzoyl chloride (5.05 g, 0.0223 mol) and 4-bromoaniline (3.83 g, 0.0223 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (4.26 mL, 0.0245 mol) was added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue was partitioned between ethyl acetate (120 mL) and water (100 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold *n*-heptane (50 mL) and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.74 (s, 1H), 7.90 (m, 2H), 7.74 (d, 1H), 7.68 (d, 2H), 7.56 (d, 2H).

B. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-

benzenecarbothioamide

A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (3.97 g, 0.0098 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica using ethyl acetate/n-heptane (1:8) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (6.0 g, 0.0159 mol) as a yellow solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 12.33 (s, 1H), 7.94 (d, 2H), 7.81 (m, 2H), 7.65 (m, 3H). TLC (ethyl acetate / heptane 1:4) R_f 0.61

C. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime

A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (2.50 g, 0.00663 mol), hydroxylamine hydrochloride (0.65 g, 0.00928 mol) and sodium bicarbonate (0.78 g, 0.00928 mol) was heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.35 g, 0.00625 mol) as an off-white solid.

TLC (ethyl acetate / heptane 1:4) R_f 0.12

D. *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine

To a solution of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.25 g, 0.00598 mol) in *N*-methylpyrrolidinone (30 mL), potassium *tert*-butoxide (0.71 g, 0.00628 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction

mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane and the precipitate was collected by filtration and dried to yield *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (1.75 g, 0.0049 mol) as an off-white solid.

¹H NMR (DMSO-*d*₆, 400MHz) δ 9.95 (s, 1H), 8.37 (d, 1H), 8.14 (s, 1H), 7.78 (d, 1H), 7.68 (d, 2H), 7.58 (d, 2H). TLC (ethyl acetate / heptane 1:5) R_f 0.31

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E. *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine

A mixture of *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (1.75 g, 0.0049 mol), diboron pinacol ester (1.49 g, 0.0059 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.120 g, 0.000147 mol) and potassium acetate (1.44 g, 0.0144 mol) in *N,N*-dimethylformamide (10 mL) was heated at 80°C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:6) as mobile phase to yield *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (0.065 g, 0.000161 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.97 (s, 1H), 8.39 (d, 1H), 8.14 (s, 1H), 7.77 (d, 1H), 7.71 (s, 4H), 1.29 (s, 12H).

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F. *Trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate

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A mixture of *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (0.062 g, 0.000153 mol), *trans*-3-

iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.065 g, 0.000146 mol), tetrakis-(triphenylphosphine)palladium (0.010 g, 0.0000087 mol) and sodium carbonate (0.039 g, 0.000365 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80 °C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8µm, 25 cm; 10-70% acetonitrile – 0.1M ammonium acetate over 30 min, 21mL/min) to yield *trans*-*N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate (0.026 g, 0.0000398 mol) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.05 (s, 1H), 8.44 (d, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.88 (d, 2H), 7.79 (d, 1H), 7.69 (d, 2H), 4.67 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H); RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 16.18 min. MS: MH⁺ 592.

Example 600: *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. 3-iodo-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (0.4 g, 0.00096 mol) and potassium carbonate (0.40 g, 0.0029 mol) in *N,N*-dimethylformamide (25 mL) was added 2-bromoethyl methyl ether (0.09 mL, 0.00096 mol) at room temperature. The heterogeneous mixture was stirred at 60 °C under an atmosphere of nitrogen for 7 hours. The reaction mixture was cooled to room temperature, and 2-bromoethyl methyl ether (0.045 mL, 0.00048 mol) was added. The mixture was stirred at 60 °C under an atmosphere of nitrogen for 16 hours. To the mixture to the room temperature, 2-bromoethyl methyl ether (0.019 mL, 0.00019 mol) and potassium iodide (0.008 g, 0.000048 mol) were added in order to complete the reaction. The mixture was stirred at 70 °C under an

atmosphere of nitrogen for 7 hours. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 50% over 30 min with 0.1 M ammonium acetate, 21mL/min) to yield 3-iodo-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.0005 mol). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile - 0.1M ammonium acetate over 10 min, 1mL/min) Rt 6.4 min. MS: MH⁺ 403

B. *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.0005 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.28 g, 0.00078 mol), tetrakis(triphenylphosphine)palladium (0.029 g, 0.000025 mol) and sodium carbonate (0.13 g, 0.00125 mol) in ethylene glycol dimethyl ether (25 mL) and water (5 mL) was heated at 80°C for 5 hours under an atmosphere of nitrogen. Additional *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.14 g, 0.00039 mol.) and tetrakis(triphenylphosphine)-palladium (0.015 g, 0.0000125 mol) were added, and the mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 20 % methanol / dichloromethane as a mobile phase to give *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-

yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.14 g, 0.00027 mol). ¹H NMR (TFA-*d*, 400 MHz) δ 8.53 (s, 1H), 7.88 (m, 2H), 7.81 (m, 2H), 7.14 (s, 2H), 5.40 (br, 1H), 4.05 (m, 2H), 3.98 (m, 2H), 3.66 (m, 2H), 3.56 (s, 3H), 3.47 (m, 2H), 2.96 (m, 2H), 2.54 (br, 2H), 2.50 (s, 3H), 2.43 (s, 3H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.6 min. MS: MH⁺ 513

Example 601: *N*2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A. 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (0.5 g, 0.0012 mol) and sodium triacetoxyborohydride (0.36 g, 0.00168 mol) in dichloroethane (40 mL) was added formaldehyde solution (37 % in water, 0.037 mL, 0.00132 mol) at room temperature. The mixture was stirred at room temperature under an atmosphere of nitrogen for 4 hours. A 5 N aqueous solution of sodium hydroxide (2 mL) was added to the mixture. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave solid. The solid was resubjected to the same reaction and work-up conditions as above to yield 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.3 g, 0.00084 mol). TLC (methanol / dichloromethane = 10 : 90) R_f 0.63 MS: MH⁺ 359

B. *N*2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.00056 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.2 g, 0.00056 mol), tetrakis(triphenylphosphine)-palladium (0.032 g, 0.000028 mol) and sodium

carbonate (0.15 g, 0.0014 mol) in ethylene glycol dimethyl ether (20 mL) and water (5 mL) was heated at 80°C for 3 hours under an atmosphere of nitrogen. Additional *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.2 g, 0.00056 mol) and tetrakis(triphenylphosphine)palladium (0.032 g, 0.000028 mol) were added, and the mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 25 % methanol / dichloromethane as a mobile phase to give *N*2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine (0.16 g, 0.00034 mol). ¹H NMR (TFA-*d*, 400 MHz) δ 8.50 (s, 1H), 7.85 (m, 2H), 7.80 (m, 2H), 7.10 (s, 2H), 5.45 (br, 1H), 3.95 (br, 2H), 3.75 (br, 1H), 3.45 (br, 1H), 3.10 (s, 3H), 2.85 (br, 1H), 2.65 (br, 1H), 2.49 (br, 2H), 2.40 (s, 3H), 2.42 (s, 3H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) Rt 10.7 min. MS: MH⁺ 469

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Example 602: *N*2-{4-[4-amino-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A. 3-Iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine

Diethyl azodicarboxylate (12 mL, 0.08 mol) was added to a stirred suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (10.44 g, 0.04 mol), *tert*-butyl 3-hydroxy-1-piperidinecarboxylate (12.0 g, 0.0596 mol), and triphenylphosphine (20.98 g, 0.08 mol) in tetrahydrofuran (600 mL) at room temperature. After 19 h, additional diethyl azodicarboxylate (12 mL, 0.08 mol) was added and the reaction was continued for a further 2 h. Additional *tert*-butyl 3-hydroxy-1-piperidinecarboxylate (2.0 g) and triphenylphosphine (20.98 g, 0.08 mol) were added and the reaction continued for a further 72 h.

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The reaction was concentrated *in vacuo*, acetone (200 mL) and an aqueous 5N solution of hydrogen chloride (100 mL) were added and the solution was heated at 40 °C for 2 h. The acetone was removed under reduced pressure and the aqueous layer was washed with dichloromethane (3 x 200 mL). The aqueous layer was then
5 basified to pH 11 with aqueous solution of sodium hydroxide (1 N) and the product was extracted into dichloromethane (3 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford an orange solid. The solid was triturated with ethyl acetate to afford 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine as a yellow solid (3.82 g, 25 %); RP-HPLC Rt
10 4.792 min, 92 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column);
¹H NMR (400 MHz, *d*₆-DMSO) 1.54 (1H, m), 1.71 (1H, m), 2.01 (2H, m), 2.46 (1H, m), 2.81 (2H, m), 3.01 (1H, dd, *J* 11.8 and 3.4 Hz), 4.58 (1H, m), and 8.19 (1H, s).

15

B. 3-iodo-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
20 (0.4 g, 0.00116 mol) and sodium triacetoxyborohydride (0.34 g, 0.00162 mol) in dichloroethane (30 mL) was added formaldehyde solution (37 % in water, 0.035 mL, 0.00128 mol, 1.1 eq.) at room temperature. The mixture was stirred at room temperature under an atmosphere of nitrogen for 18 hours. Additional formaldehyde solution (37 % in water, 0.035 mL, 0.00128 mol, 1.1 eq.) was added, and the
25 mixture was stirred at room temperature for 2 hours. A 5 N aqueous solution of sodium hydroxide (5 mL) was added to the mixture. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic extracts were washed with water, and brine, and dried
30 over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the mixture was lyophilized to yield 3-iodo-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.41 g, 0.0011 mol). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min,

1mL/min) Rt 6.0 min. MS: MH⁺ 359

C. *N*2-{4-[4-amino-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

5 A mixture of 3-iodo-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.35 g, 0.001 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.44 g, 0.0012 mol), tetrakis(triphenylphosphine)-palladium (0.058 g, 0.00005 mol) and sodium carbonate (0.27 g, 0.0025 mol) in ethylene glycol dimethyl ether (30 mL) and water
10 (6 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous
15 sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 2 % - 10 % methanol / dichloromethane as a mobile phase to give *N*2-{4-[4-amino-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-
20 2-amine (0.055 g, 0.00012 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.80 (s, 1H), 8.22 (s, 1H), 7.95 (d, 2H), 7.65 (d, 2H), 7.15 (s, 1H), 6.80 (s, 1H), 4.80 (br, 1H), 2.95 (br, 1H), 2.85 (br, 1H), 2.45 (br, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H), 2.00 (br, 3H), 1.80 (br, 1H), 1.70 (br, 1H). RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt
25 9.7 min. MS: MH⁺ 469

Example 603: *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

30 A. 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

(0.4 g, 0.00116 mol) and potassium carbonate (0.48 g, 0.00348 mol) in *N,N*-dimethylformamide (25 mL) were added 2-bromoethyl methyl ether (0.11 mL, 0.00116 mol) and potassium iodide (0.010 g, 0.000058 mol) at room temperature. The mixture was stirred at 65 °C under an atmosphere of nitrogen for 16 hours. The reaction mixture was cooled to room temperature, and additional 2-bromoethyl methyl ether (0.025 mL, 0.00027 mol) was added. The mixture was stirred at 65 °C under an atmosphere of nitrogen for 16 hours. The solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. The residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 50% over 30 min with 0.1 M ammonium acetate, 21 mL/min) to 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.2 g, 0.0005 mol). TLC (methanol / dichloromethane = 10 : 90) R_f 0.5 MS: MH^+ 403

B. *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

The mixture of 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.16 g, 0.0004 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.17 g, 0.00048 mol), tetrakis(triphenylphosphine)palladium (0.023 g, 0.00002 mol) and sodium carbonate (0.11 g, 0.001 mol) in ethylene glycol dimethyl ether (25 mL) and water (5 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 2 % - 10 % methanol / dichloromethane as a mobile phase to give *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-

3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.17 g, 0.00033 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.85 (s, 1H), 8.22 (s, 1H), 7.95 (d, 2H), 7.65 (d, 2H), 7.14 (s, 1H), 6.80 (s, 1H), 4.79 (br, 1H), 3.50 (m, 2H), 3.25 (s, 3H), 3.10 (br, 1H), 2.90 (br, 1H), 2.55 (br, 2H), 2.54 (br, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.05 (br, 3H), 1.80 (br, 1H), 1.70 (br, 1H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.9 min. MS: MH⁺ 513

Example 604: *N*2-{4-[4-amino-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine acetate

A. *tert*-Butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

Di-*tert*-butyl dicarbonate (2.093 g, 0.00959 mol) was added to a solution of 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (3.00 g, 0.00872 mol) and sodium carbonate (3.23 g, 0.0305 mol) in 1,4-dioxane (50 mL) and water (50 mL). The mixture was stirred at room temperature for 2 h and the resulting white precipitate was collected by filtration. The solid was washed with water (10 mL) and dried in air to afford *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate as a white solid (3.40 g, 88 %); RP-HPLC Rt 12.532 min, 98 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ¹H NMR (400 MHz, *d*₆-DMSO) 1.34 (9H, br s), 1.50 (2H, m), 2.02 (1H, m), 2.13 (1H, m), 2.97 (2H, m), 3.85 (2H, m), 4.59 (1H, m), and 8.21 (1H, s).

B. *tert*-Butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

The mixture of *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.6 g, 0.00135 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.59 g, 0.00162 mol), tetrakis(triphenylphosphine)palladium (0.078 g, 0.000068 mol) and sodium

carbonate (0.36 g, 0.00338 mol) in ethylene glycol dimethyl ether (50 mL) and water (10 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. After cooled the mixture to the room temperature, more *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.24 g, 0.00066 mol), tetrakis(triphenylphosphine)palladium (0.078 g, 0.000068 mol) were added, and the mixture was stirred at 80 °C for 5 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish oil which was purified by flash column chromatography on silica using 5 % - 25 % isopropanol / dichloromethane as a mobile phase, and the product was triturated with *N,N*-dimethylformamide to give *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.28 g, 0.00051 mol). RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.9 min.

MS: MH⁺ 555

C. *N*2-{4-[4-amino-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine acetate

To a mixture of *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.28 g, 0.00051 mol) in acetone (10 mL) was added an 6N aqueous solution of hydrogen chloride (3 mL) at room temperature. The mixture was stirred at 45 °C for 1 hour. The solvent was removed, and the mixture was basified with an aqueous 5N sodium hydroxide solution. The aqueous layer was extracted with dichloromethane (3 x 80 mL). The solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8μm, 250 x 21.1 mm; 5% - 100% over 20 min with 0.1 M ammonium acetate, 21mL/min) to yield *N*2-{4-[4-amino-1-(3-piperidyl)-

1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine acetate (0.06 g, 0.00012 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.85 (s, 1H), 8.22 (s, 1H), 7.95 (d, 2H), 7.65 (d, 2H), 7.05 (s, 1H), 6.80 (s, 1H), 4.75 (br, 1H), 3.15 (br, 2H), 2.95 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 2.05 (br, 1H), 2.00 (br, 1H), 1.90 (s, 3H), 1.80 (br, 1H), 1.60 (br, 1H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.4 min. MS: MH⁺ 455

Example 605: 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-(dimethylamino)-1-ethanone acetate

A mixture of *N*2-{4-[4-amino-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine acetate (0.04 g, 0.000078 mol), dimethylglycine (0.01 g, 0.000097 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.019 g, 0.000097mol), *N,N*-diisopropylethylamine (0.033g, 0.00026 mol) and 1-hydroxy-7-azabenzotriazole (0.011 g, 0.000078 mol) in anhydrous dichloromethane (5 mL) was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organic solvent was washed with brine. The solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 35 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-(dimethylamino)-1-ethanone acetate (0.015 g, 0.00003 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.85 (s, 1H), 8.27 (d, 1H), 7.94 (d, 2H), 7.67 (d, 2H), 7.11 (s, 1H), 6.51 (s, 1H), 4.81 – 1.91 (br, 11 H), 2.40 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H), 1.91 (s, 3H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.7 min. MS: MH⁺ 540

Example 606: 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone

5 A. 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride

To a mixture of *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (1.2 g, 0.0027 mol) in acetone (20 mL) was added an aqueous 6N solution of hydrogen chloride (8 mL) at room temperature. The mixture was stirred at 45 °C for 1.5 hours, and then room temperature for 16 hours. The precipitate was filtered and washed with acetone. The solid was dried to give 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (1 g, 0.0024 mol). TLC (methanol / dichloromethane = 5 : 95) *R*_f 0.14 MS: MH⁺ 345

15 B. 9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate

A mixture of 3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (0.17g, 0.00042 mol), 2-[(9*H*-9-fluorenylmethoxy)carbonyl]-(methylamino)-2-methylpropanoic acid (0.175 g, 0.00052 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.1 g, 0.00052 mol), *N,N*-diisopropylethylamine (0.23 g, 0.0018 mol) and 1-hydroxy-7-azabenzotriazole (0.057 g, 0.00042 mol) in anhydrous dichloromethane (7 mL) was stirred for 18 hours at room temperature. Additional 2-[(9*H*-9-fluorenylmethoxy)carbonyl](methylamino)-2-methylpropanoic acid (0.044 g, 0.00013 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.025 g, 0.00013 mol) were added to the reaction and stirred for 16 hours. The solvent was removed under reduced pressure. The residue was partitioned between brine and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8μm, 250 x 21.1 mm; 5% - 100% over 20 min with 0.1 M ammonium acetate, 21mL/min) to yield 9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate (0.030g, 0.00005 mol). RP-HPLC (Delta Pak C18,

5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.2 min. MS: MH⁺ 666

5 C. 9*H*-9-fluorenylmethyl *N*-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate

A mixture of 9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate (0.03 g, 0.000045 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.02 g, 0.000054 mol), tetrakis(triphenylphosphine)-palladium (0.003 g, 0.000002 mol) and sodium carbonate (0.0126 g, 0.00011mol) in ethylene glycol dimethyl ether (4 mL) and water (1 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid, which was carried to the next reaction. RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.4 min. TLC (methanol / dichloromethane = 5 : 95) R_f 0.80

25 D. 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone

A crude mixture of 9*H*-9-fluorenylmethyl *N*-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate (0.037 g, 0.00005 mol) in a 25 % solution of piperidine in *N,N*-dimethylformamide (10 mL) was stirred for 16 hours at room temperature under an atmosphere of nitrogen. The solvent was removed, and the residue was partitioned between ethyl acetate and water. The

combined organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 30 min with 0.1 M ammonium acetate, 21mL/min) to yield 1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone (0.011g, 0.00002 mol). ¹H NMR (Chloroform-*d*, 400 MHz) δ 8.35 (s, 1H), 7.75 (m, 2H), 7.40 (m, 2H), 7.10 (s, 1H), 6.78 (s, 1H), 4.98 – 1.70 (br, 9 H), 2.49 (s, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 2.10 (s, 6H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.0 min. MS: MH⁺ 554

Example 607: *N*2-4-[4-amino-1-(3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *tert*-Butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate

A mixture of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.73 g, 0.0028mol), *tert*-butyl 3-[(methylsulfonyl)oxy]-1-azetanecarboxylate (1.05 g, 0.0042 mol) and cesium carbonate (1.4 g, 0.0042 mol) in *N,N*-dimethylformamide (25 mL) were stirred at 70 °C under an atmosphere of nitrogen for 16 hours. The mixture was cooled to room temperature. Additional *tert*-butyl 3-[(methylsulfonyl)oxy]-1-azetanecarboxylate (0.35 g, 0.0014 mol) and cesium carbonate (0.46 g, 0.0014 mol) were added to the mixture. The mixture was stirred at 70 °C under an atmosphere of nitrogen for 16 hours. The solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with dichloromethane (3 x 70 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. The residue was triturated with dichloromethane (2 x 3 mL) to give *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate (0.57 g, 0.0014 mol). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.4 min. MS: MH⁺ 417

B. *tert*-Butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate

A mixture of *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate (0.15 g, 0.00036 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.16 g, 0.00045 mol), tetrakis(triphenylphosphine)palladium (0.021 g, 0.000018 mol) and sodium carbonate (0.095 g, 0.0009 mol) in ethylene glycol dimethyl ether (5 mL) and water (2 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The reaction was cooled to room temperature. Additional tetrakis(triphenylphosphine)palladium (0.021 g, 0.000018 mol) was added to the mixture. The reaction was stirred at 80 °C for 3 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 50 % methanol / dichloromethane as a mobile phase to give *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate (0.033 g, 0.00006 mol). RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.6 min. MS: MH⁺ 527

C. *N*2-4-[4-amino-1-(3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine

To a mixture of *tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate (0.033 g, 0.000063 mol) in acetone (4 mL) was added an aqueous 6N solution of hydrogen chloride (0.3 mL) at room temperature. The mixture was stirred at 45 °C for 2 hour, and then at room temperature for 16 hours. The solid from the reaction

was filtered and washed with acetone. In order to remove some impurities, the solid was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with brine. The solvent was removed to yield *N*2-4-[4-amino-1-(3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine (0.004 g, 0.00001 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.85 (s, 1H), 8.45 (s, 1H), 8.00 (d, 2H), 7.75 (d, 2H), 7.09 (s, 1H), 6.80 (s, 1H), 5.90 (br, 1H), 5.20 (m, 4H), 2.40 (s, 3H), 2.20 (s, 3H).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.1 min. MS: MH⁺ 427

Example 608: *N*2-{4-[4-amino-1-(1-methyl-3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A. 1-(3-azetanyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

A mixture of *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-azetanecarboxylate (0.41 g, 0.00099 mol) in acetone (5 mL) was added an aqueous 6N solution of hydrogen chloride (1 mL) at room temperature. The mixture was stirred at 45 °C for 2 hour. The solvent was removed under reduced pressure, and the residue was basified with an aqueous 5N solution of sodium hydroxide at 0 °C. The aqueous layer was extracted with dichloromethane (3 x 50 mL), and the organic layer was washed with brine and dried under magnesium sulfate. The solvent was removed under reduced pressure. The aqueous layer and the residue from organic layer were combined. The solvents were removed, and the residue was suspended in *N,N*-dimethylformamide, methanol, and acetic acid and purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 100% over 30 min with 0.1 M ammonium acetate, 21mL/min) to 1-(3-azetanyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.165 g, 0.0005 mol).

TLC (methanol/dichloromethane 5:95) R_f 0.29. MS: MH⁺ 317

B. 3-iodo-1-(1-methyl-3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of to 1-(3-azetanyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-

amine diacetate (0.165 g, 0.0005 mol) and sodium triacetoxyborohydride (0.15 g, 0.00073 mol) in dichloroethane (15 mL) was added a 37% solution of formaldehyde in 0.016 mL, 0.000572 mol) at room temperature. The mixture was stirred at room temperature under an atmosphere of nitrogen for 16 hours. Additional formaldehyde (37 % in water, 0.016 mL, 0.000572 mol) and sodium triacetoxyborohydride (0.15 g, 0.00073 mol) were added, and the mixture was stirred at room temperature for 2 days. An aqueous 5N solution of sodium hydroxide (1 mL) was added to the mixture. The solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure. Majority product was still in aqueous layer. The aqueous layer and the residue from organic layer were combined. The solvent was removed, and the residue was carried to the next step without purification. TLC (methanol / dichloromethane = 10 : 90) R_f 0.48 MS: MH^+ 331

C. *N*2-{4-[4-amino-1-(1-methyl-3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-(1-methyl-3-azetanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.17 g, 0.00052 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.23 g, 0.000624 mol), tetrakis(triphenylphosphine)-palladium (0.030 g, 0.000026 mol) and sodium carbonate (0.14 g, 0.0013 mol) in ethylene glycol dimethyl ether (20 mL) and water (15 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The reaction was cooled to room temperature. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish solid which was purified by flash column chromatography on silica using 5 % - 50 % methanol / dichloromethane as a mobile phase to give *N*2-{4-[4-amino-1-(1-methyl-3-azetanyl)-1*H*-pyrazolo[3,4-

d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine (0.13 g, 0.0003 mol).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.85 (s, 1H), 8.15 (s, 1H), 7.90(d, 2H), 7.70 (d, 2H), 7.09(s, 1H), 6.85(s, 1H), 5.40 (br, 1H), 3.90 (m, 2H), 3.70 (m, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.5 min. MS: MH⁺ 441

Example 609: *Cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile

A. 3-amino-4-hydroxybenzonitrile

To a mixture of 4-hydroxy-3-nitrobenzonitrile (4 g, 0.0244 mol) in ethanol (180 mL) and water (90 mL) was added sodium thiosulfate (17 g, 0.0976 mol) at room temperature. The heterogeneous mixture was stirred at 80 °C under an atmosphere of nitrogen for 1 hour. The reaction mixture was cooled to room temperature, and ethanol was removed under reduced pressure. The yellow solid was filtered, washed with water, and dried under reduced pressure to yield 3-amino-4-hydroxybenzonitrile (1.46 g, 0.011 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 4.5 min. MS: MH⁺: 133

B. 2-(4-bromoanilino)-1,3-benzoxazole-5-carbonitrile

To a mixture of 3-amino-4-hydroxybenzonitrile (1.84 g, 0.0137 mol) in acetonitrile (140 mL) was added 4-bromophenyl isothiocyanate (2.93 g, 0.0137 mol) at room temperature. The mixture was stirred for 16 hours at room temperature. Cuprous chloride (1.36 g, 0.0137 mol) and triethylamine (1.9 mL, 0.0137 mol) were added to the reaction mixture. The mixture was stirred for 16 hours at room temperature. The solvent was removed under reduced pressure, and the solid was suspended in methanol. The mixture was filtered through celite pad using methanol. The brownish filtrate was left at 4° for three days. The precipitate was filtered and washed with methanol to yield 2-(4-bromoanilino)-1,3-benzoxazole-5-carbonitrile

(2.4 g, 0.0076 mol). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.1 min. MS: MH⁺: 313

5 C. 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile

A mixture of 2-(4-bromoanilino)-1,3-benzoxazole-5-carbonitrile (1.8 g, 0.0058mol), diboron pinacol ester (1.8 g, 0.007 mol), [1.1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with
10 dichloromethane (1:1) (0.47g, 0.00058 mol) and potassium acetate (1.7 g, 0.0174 mol) in *N,N*-dimethylformamide (50 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica using 0 % - 40 % ethyl acetate / n-heptane as a
15 mobile phase to give 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile (0.80 g, 0.0022 mol). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) Rt 16.9 min. MS: MH⁺: 362

20 D. *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile

A mixture of 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.15 g, 0.00034 mol), 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile (0.153 g, 0.000425 mol),
25 tetrakis(triphenylphosphine)palladium (0.028 g, 0.0000238 mol) and sodium carbonate (0.090g, 0.00085 mol) in ethylene glycol dimethyl ether (3 mL) and water (1 mL) was heated at 80°C for 16 hours. Additional 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1,3-benzoxazole-5-carbonitrile (0.072g, 0.0002 mol),
30 tetrakis(triphenylphosphine)palladium (0.012 g, 0.000010 mol, 0.03 eq.) were added, and the mixture was stirred at 80 °C for 16 hours under atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was

removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the residue was purified by flash column chromatography on silica using 2 % aqueous ammonium hydroxide solution / 5 % - 20 % methanol / dichloromethane as a mobile phase. The solvent was removed under reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8 μ m, 250 x 21.1 mm; 5% - 50% over 30 min with 0.1 M ammonium acetate, 21mL/min) to give *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile (0.15g, 0.00027 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.25 (s, 1H), 8.53 (s, 1H), 8.00 (s, 1H), 7.95 (d, 2H), 7.70(m, 4H), 4.80 (br, 1H), 2.49 (s, 3H), 2.20 (br, 8H), 2.10 (br, 3H), 1.75 (br, 2H), 1.60 (br, 4H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 9.2 min. MS: MH⁺ 549.

Example 610: *Cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

A. 2-nitro-4-(trifluoromethoxy)phenol

To a mixture of 4-(trifluoromethoxy)phenol (4 g, 0.0225mol) in ethylene glycol dimethyl ether (90 mL) was added a 0.5 M solution of nitronium tetrafluoroborate in sulfolane (46 mL, 0.0229 mol) at –50 °C. The mixture was stirred at –50 °C under an atmosphere of nitrogen for 6 hours. The mixture was filtered through silica gel pad, and the pad was washed with 25 % ethyl acetate / n-heptane. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and brine. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica using 0 % - 50 % ethyl acetate / n-heptane as a mobile phase to give 2-nitro-4-(trifluoromethoxy)phenol (2.5 g, 0.011 mol). TLC (ethyl

acetate / n-heptane = 25 : 75) R_f 0.50 MS: MH⁺: 222

B. 2-amino-4-(trifluoromethoxy)phenol

To a mixture of 2-nitro-4-(trifluoromethoxy)phenol (2 g, 0.0089 mol) in
5 ethanol (50 mL) and water (25 mL) was added sodium thiosulfate (6.2 g, 0.0356
mol) at room temperature. The heterogeneous mixture was stirred at 80 °C under an
atmosphere of nitrogen for 1 hour. The reaction mixture was cooled to room
temperature, and ethanol was removed under reduced pressure. The aqueous layer
was extracted with ethyl acetate (3 x 70 mL), and the organic layer was washed with
10 brine and dried under sodium sulfate. The solvent was removed under reduced
pressure to give yellow solid of 2-amino-4-(trifluoromethoxy)phenol (0.9 g, 0.005
mol). TLC (methanol / dichloromethane = 5 : 95) R_f 0.29 MS: MH⁺: 194

C. N2-(4-bromophenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

To a mixture of 2-amino-4-(trifluoromethoxy)phenol (0.9 g, 0.0047 mol) in
15 tetrahydrofuran (60 mL) was added 4-bromophenyl isothiocyanate (1 g, 0.0047 mol)
at room temperature. The mixture was stirred for 16 hours at room temperature.
Anhydrous copper sulfate (7.1 g, 0.0443 mol, 9.43 eq.), triethylamine (0.67 mL,
0.0047 mol, 1 eq.), and silica gel (8.5 g) were added to the reaction mixture. The
20 mixture was stirred for 4 hours at room temperature. The solvent was removed
under reduced pressure. The mixture was filtered through silica gel pad using 25 %
ethyl acetate / n-heptane as a mobile phase to give orange colored solid. The solid
was purified by flash column chromatography on silica using 0 % - 25 % ethyl
acetate / n-heptane as a mobile phase. The solvent was removed, and the residue
25 was triturated with n-heptane to give N2-(4-bromophenyl)-5-(trifluoromethoxy)-1,3-
benzoxazol-2-amine (0.9 g, 0.0024 mol).

RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M
ammonium acetate over 10 min, 1mL/min) Rt 12.2 min. MS: MH⁺: 373

30 D. N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-
(trifluoromethoxy)-1,3-benzoxazol-2-amine

A mixture of N2-(4-bromophenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-
amine (0.9 g, 0.0024 mol), diboron pinacol ester (0.73 g, 0.0029 mol), [1.1'-

bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1) (0.2 g, 0.00024 mol) and potassium acetate (0.71 g, 0.0072 mol) in *N,N*-dimethylformamide (25 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The residue was filtered through silica pad 25 % ethyl acetate / n-heptane as a mobile phase. The solvent was removed, and the residue was triturated with n-heptane to give *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.68 g, 0.0016 mol). RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) Rt 18.8 min. MS: MH⁺: 421

E. *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.06g, 0.00014 mol), *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.071 g, 0.00017 mol), tetrakis(triphenylphosphine)palladium (0.011 g, 0.00001 mol) and sodium carbonate (0.037, 0.00035 mol) in ethylene glycol dimethyl ether (3 mL) and water (1 mL) was heated at 80°C for 16 hours. Additional *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.030 g, 0.00007 mol) and tetrakis(triphenylphosphine)palladium (0.005 g, 0.000004 mol) were added, and the mixture was stirred at 80 °C for 5 hours under atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the residue was purified by flash column chromatography on silica using 2 % aqueous ammonium hydroxide solution / 5 % - 25 % methanol / dichloromethane as a mobile phase. The solvent was removed under reduced pressure to give *cis-N*2-(4-

{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.065 g, 0.00011 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.25 (s, 1H), 8.20 (s, 1H), 7.95 (d, 2H), 7.65 (m, 3H), 7.50 (s, 1H), 7.15 (s, 1H), 4.80 (br, 1H), 2.60 (br, 9H), 2.49 (s, 3H), 2.20 (br, 3H), 2.10 (br, 1H), 1.75 (br, 2H), 1.60 (br, 2H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.7 min. MS: MH⁺ 608

Example 611: *Cis*- *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine

A. 4-ethyl-2-nitrophenol

To a mixture of 4-ethylphenol (4 g, 0.0328mol) in ethylene glycol dimethyl ether (100 mL) was added a 0.5 M solution of nitronium tetrafluoroborate in sulfolane (67 mL, 0.0335 mol) at –50 °C. The mixture was stirred at –50 °C under the atmosphere of nitrogen for 6 hours. The mixture was filtered through silica gel pad, and the pad was washed with 25 % ethyl acetate / n-heptane. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and brine. The solvent was removed under reduced pressure to give about 10 g of crude 4-ethyl-2-nitrophenol. The crude material was used in the next step without purification.

¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.68 (s, 1H), 7.71 (s, 1H), 7.40 (d, 1H), 7.07 (d, 1H), 2.60 (q, 2H), 1.20 (t, 3H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.2 min.

B. 2-amino-4-ethylphenol

To a mixture of 4-ethyl-2-nitrophenol (5.5 g, 0.032 mol) in ethanol (180 mL) and water (90 mL) was added sodium thiosulfate (23 g, 0.131 mol) at room temperature. The heterogeneous mixture was stirred at 80 °C under an atmosphere of nitrogen for 16 hour. The reaction mixture was cooled to room temperature, and ethanol was removed under reduced pressure. The aqueous layer was extracted with

ethyl acetate (3 x 100 mL), and the organic layer was washed with brine and dried under sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica using 0 % - 25 % methanol / dichloromethane as a mobile phase (x 2). The solvent was removed under reduced pressure to give 2-amino-4-ethylphenol (0.89 g, 0.006 mol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.61 (br, 2H), 6.47 (d, 1H), 6.37 (s, 1H), 6.18 (d, 1H), 2.17 (q, 2H), 1.08 (t, 3H). MS: MH⁺: 137

C. *N*2-(4-bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine

To a mixture of 2-amino-4-ethylphenol (0.89 g, 0.0065 mol) in tetrahydrofuran (80 mL) was added 4-bromophenyl isothiocyanate (1.4 g, 0.0065 mol) at room temperature. The mixture was stirred for 2 hours at room temperature. Anhydrous copper sulfate (6.2 g, 0.039 mol), triethylamine (0.9 mL, 0.0065 mol) and silica gel (11.7 g) were added to the reaction mixture. The mixture was stirred for 4 hours at room temperature. The solvent was removed under reduced pressure. The mixture was filtered through silica gel pad using 25 % ethyl acetate / n-heptane as a mobile phase to give brown colored solid. The solid was purified by flash column chromatography on silica using 0 % - 25 % ethyl acetate / n-heptane as a mobile phase. The solvent was removed, and the residue was triturated with n-heptane to give *N*2-(4-bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.96 g, 0.003 mol). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 12.1 min. MS: MH⁺: 318

D. *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-ethyl-1,3-benzoxazol-2-amine

A mixture of *N*2-(4-bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.86 g, 0.0027 mol), diboron pinacol ester (0.84 g, 0.0033 mol), [1.1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1) (0.22 g, 0.00027 mol) and potassium acetate (0.8 g, 0.0081 mol) in *N,N*-dimethylformamide (30 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature

and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the organic layer was washed with brine. The solvent was removed under reduced pressure, and the crude material was purified by flash column

5 chromatography on silica using 0 % - 25 % ethyl acetate / n-heptane as a mobile phase to give *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-ethyl-1,3-benzoxazol-2-amine (0.82 g, 0.002 mol).

TLC (ethyl acetate / n-heptane = 25 : 75) R_f 0.30. MS: MH^+ : 365

10 E. *cis*- *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine

A mixture of 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.06g, 0.00014 mol), *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-
15 dioxaborolan-2-yl)phenyl]-5-ethyl-1,3-benzoxazol-2-amine (0.062 g, 0.00017 mol), tetrakis(triphenylphosphine)palladium (0.011 g, 0.00001 mol) and sodium carbonate (0.037, 0.00035 mol) in ethylene glycol dimethyl ether (3 mL) and water (1 mL) was heated at 80°C for 16 hours. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue
20 was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure, and the residue was purified by flash column chromatography on silica using 2 %
25 aqueous ammonium hydroxide solution / 5 % - 25 % methanol / dichloromethane as a mobile phase. The solvent was removed under reduced pressure to give *cis*- *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.065g, 0.00012 mol). 1H NMR (DMSO-*d*₆, 400 MHz) δ 11.25 (s, 1H), 8.65 (s, 1H), 8.37 (d, 2H), 8.09 (d, 2H), 7.84
30 (d, 1H), 7.76 (s, 1H), 7.42 (d, 1H), 5.22 (br, 1H), 3.13 (q, 2H), 2.52 (br, 7H), 2.69 (br, 4H), 2.64 (s, 3H), 2.49 (br, 2H), 2.11 (br, 2H), 2.01 (br, 2H), 1.63 (t, 3H). RP-HPLC (Delta Pak C18, 5 μ m, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium

acetate over 10 min, 1mL/min) Rt 10.3 min. MS: MH⁺ 552

Examples 612: *Cis-N2*-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine; and

Example 613: *Cis-N2*-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *Cis*- and *trans*-1-[4-(dimethylamino)cyclohexyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Sodium triacetoxyborohydride (1.40 g, 6.61 mmol) was added to a solution of 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-cyclohexanone monohydrochloride (2.00 g, 5.08 mmol), dimethylamine solution (2 M in tetrahydrofuran, 7.62 mL, 15.24 mmol) and acetic acid (0.87 mL, 15.24 mmol) in 1,2-dichloroethane (200 mL) at room temperature. The reaction was stirred for 24 h and additional sodium triacetoxyborohydride (0.40g) was added. After a further 24h, saturated aqueous NaHCO₃ (50 mL) and CH₂Cl₂ (200 mL) were added and the organic layer was separated, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The product was purified by column chromatography using a 1:5:94 aqueous ammonium hydroxide : MeOH : CH₂Cl₂ to 1 : 20 : 79 94 aqueous ammonium hydroxide : MeOH : CH₂Cl₂ gradient as the eluent to afford a mixture of *cis*- and *trans*-1-[4-(dimethylamino)cyclohexyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a white crystalline solid (0.87 g, 44 %); RP-HPLC Rt 5.458 min, 33 % purity, *trans*-isomer; Rt 5.621 min, 67 % purity, *cis*-isomer (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 387 (MH⁺) was observed for both the *cis*- and the *trans*-isomers.

B. *Cis*- and *trans-N2*-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of *cis*- and *trans*-1-[4-(dimethylamino)cyclohexyl]-3-iodo-1H-

pyrazolo[3,4-d]pyrimidin-4-amine (0.50 g, 1.29 mmol), *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.565 g, 1.55 mmol), sodium carbonate (0.34 g, 3.24 mmol), and *tetrakis*(triphenylphosphine) palladium (0) (0.075 g, 0.06 mmol) in ethylene glycol dimethylether (150 mL) and water (25 mL) was heated at 80 °C for 16 h. Additional Pd catalyst (0.075 g) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.40 g) were added and the reaction was continued at 80 °C for a further 16 h. Further quantities of the Pd catalyst (0.020 g) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.12 g) were added and the reaction was continued at 80 °C for a further 16 h. The reaction was concentrated *in vacuo* and the residues were dissolved in dichloromethane (200 mL) and washed with water (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using 1 % aqueous ammonium hydroxide and 10% methanol in CH₂Cl₂ as the eluent to afford *cis*- *N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.08 g), a mixed fraction (0.24 g) and *trans*-*N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.030 g); RP-HPLC Rt 11.326 min, 100 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); *m/z* 497 (MH⁺); ¹H NMR (400 MHz, *d*₆-DMSO) 1.49 (2H, *m*), 2.01 (6H, *m*), 2.33 (7H, *m*), 2.35 (3H, *s*), 2.40 (3H, *s*), 4.67 (1H, *m*), 6.80 (1H, *s*), 7.11 (1H, *s*), 7.65 (2H, *d*, *J* 8.5 Hz), 7.92 (2H, *d*, *J* 8.5 Hz), 8.23 (1H, *s*), and 10.85 (1H, *s*).

The *cis*-fraction required further purification by RP HPLC to afford *cis*-*N*2-(4-{4-amino-1-[4-(dimethylamino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.050 g), RP-HPLC Rt 11.337 min, 100 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ¹H NMR (400 MHz, *d*₆-DMSO) 1.61 (4H, *m*), 2.08 (2H, *m*), 2.27 (9H, *m*), 2.34 (3H, *s*), 2.40 (3H, *s*), 4.81 (1H, *m*), 6.80 (1H, *s*), 7.11 (1H, *s*), 7.65 (2H, *d*, *J*

8.5 Hz), 7.92 (2H, *d*, *J* 8.5 Hz), 8.23 (1H, *s*), and 10.85 (1H, *s*).

Exempls 614-620

5 The following is a general synthesis of analogs of *cis-N*2-4-[4-amino-1-(4-aminocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-1,3-benzoxazol-2-amine. Examples 614-620 were prepared using this method.

A. *N*2-(4-Bromophenyl)-5-chloro-1,3-benzoxazol-2-amine

10 4-Bromophenyl isothiocyanate (3.639 g, 17.00 mmol) was added to a solution of 2-amino-4-chlorophenol (2.441 g, 17.00 mmol) in acetonitrile (20 mL) and the reaction was stirred at room temperature for 2 h. The resulting brown solution was then added dropwise, via a dropping funnel, to a suspension of potassium superoxide (6.04 g, 85.0 mmol) in acetonitrile (20 mL) pre-cooled to 0 °C
15 in an ice bath. After 20 minutes the initial exotherm had subsided and the reaction was allowed to warm to room temperature for 40 minutes. Water (120 mL) was added dropwise and the resulting off-white solid was collected by filtration, washed with additional water (60 mL) and dried overnight on a lyophilizer to afford *N*2-(4-bromophenyl)-5-chloro-1,3-benzoxazol-2-amine as an off-white solid (4.06 g, 74 %);
20 RP-HPLC Rt 17.229 min, 99 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); *m/z* 321 (M-H)⁺ and 323 (M-H)⁺; ¹H NMR (400 MHz, *d*₆-DMSO) 7.17 (1H, *dd*, *J* 8.5 and 1.9 Hz), 7.53 (4H, *m*), 7.71 (2H, *d*, *J* 8.8 Hz), and 10.95 (1H, *s*).

25

B. *N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-chloro-1,3-benzoxazol-2-amine

 A mixture containing *N*2-(4-bromophenyl)-5-chloro-1,3-benzoxazol-2-amine (4.00 g, 12.36 mmol), *bis*(pinacolato)diboron (3.77 g, 14.83 mmol), potassium
30 acetate (3.64 g, 37.09 mmol) and [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium (II) complexed with dichloromethane (1 : 1) (0.61 g, 0.74 mmol) in dimethylformamide (200 mL) was heated at 80 °C under nitrogen for 16 h. Additional Pd catalyst (0.61 g) was added

and the reaction was continued for a further 6 h. Additional diboron (3.0 g) was then added and the reaction proceeded for a further 16 h. Silica gel (20 mL) was added to the reaction mixture and the solvent removed under reduced pressure. The resulting solid was then purified through a silica pad using a 10% to 20% ethyl acetate in heptane gradient as the eluent. The resulting solid was triturated with heptane to afford N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-chloro-1,3-benzoxazol-2-amine as a cream solid (2.40 g, 52 %); RP-HPLC Rt 18.164 min, 99 % purity (5 % to 85 % acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ¹H NMR (400 MHz, *d*₆-DMSO) 1.29 (12H, *s*), 7.17 (1H, *dd*, *J* 8.5 and 2.1 Hz), 7.56 (2H, *m*), 7.68 (2H, *m*), 7.75 (2H, *m*), and 10.96 (1H, *s*).

C. N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine

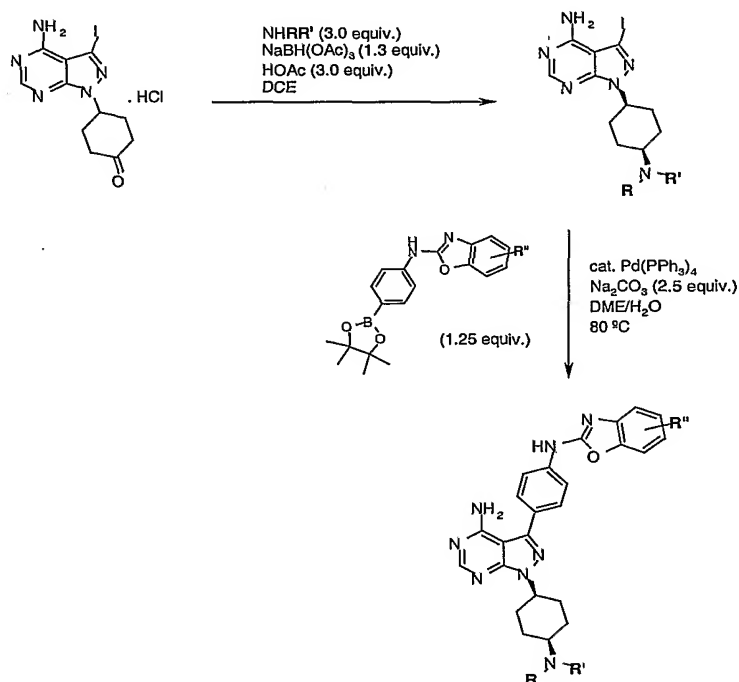
2-Amino-4-methylphenol (1.15 g, 9.34 mmol) was added to a solution of 4-bromophenyl isothiocyanate (2.00 g, 9.34 mmol) in tetrahydrofuran (35 mL) and the reaction was stirred at room temperature for 16 h. Anhydrous copper (II) sulfate (14.06 g, 88.10 mmol), silica gel (14.06 g), and triethylamine (1.3 mL, 9.34 mmol) were added, and the mixture was stirred at room temperature for 24 h. The reaction was concentrated under reduced pressure and then added to a silica pad and purified using 1 : 5 ethyl acetate : heptane (2 L) followed by diethyl ether as the eluent to afford N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine as a light brown solid (2.30 g, 81 %); RP-HPLC Rt 16.437 min, 94% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ¹H NMR (400 MHz, *d*₆-DMSO) 2.37 (3H, *s*), 6.94 (1H, *d*, *J* 8.1 Hz), 7.27 (1H, *s*), 7.36 (1H, *d*, *J* 8.1 Hz), 7.54 (2H, *d*, *J* 8.4 Hz), 7.72 (2H, *d*, *J* 8.4 Hz), and 10.72 (1H, *s*).

D. N2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-methyl-1,3-benzoxazol-2-amine

N2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-methyl-1,3-benzoxazol-2-amine was prepared from N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine (1.5 g, 4.95 mmol) using the method described for the preparation of N2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-chloro-

1,3-benzoxazol-2-amine. The product was formed as white flocculent solid (0.79 g, 46 %); RP-HPLC Rt 17.382 min, 98% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (400 MHz, d_6 -DMSO) 1.29 (12 H, s), 2.38 (3H, s), 6.94 (1H, d, J 8.1 Hz), 7.30 (1H, s), 7.36 (1H, d, J 8.1 Hz), 7.67 (2H, d, J 8.5 Hz), 7.75 (2H, d, J 8.5 Hz), and 10.74 (1H, s).

E. General synthesis of cyclohexyl amine analogs of cis-1-(4-aminocyclohexyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine



10

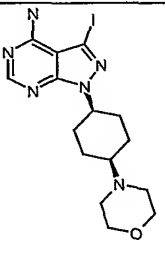
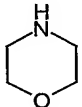
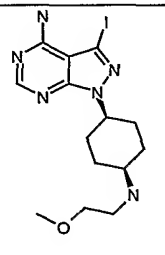
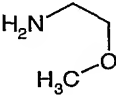
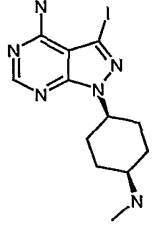
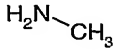
4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanone monohydrochloride (5.08-7.62 mmol scale) was suspended in dichloroethane (200-300 mL) under a nitrogen atmosphere. The appropriate amine (3.0 equivalents), glacial acetic acid (3.0 equivalents) and sodium triacetoxyborohydride (1.3 equivalents) were added and the reaction was stirred at ambient temperature for 1-2 days. For the reactions which had not gone to completion, additional sodium triacetoxyborohydride (1.3 equivalents) was added and the reaction was continued

for a further 1 or 2 days. The reactions were quenched with saturated sodium carbonate solution (50-75 mL) and extracted with dichloromethane (200-300 mL). The organic phase was separated, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to yield a mixture of *cis*- and *trans*-products as a white solid. The crude

5 products were purified via flash column chromatography using a gradient of 2% methanol and 0.2% ammonium hydroxide in dichloromethane to 5% methanol and 0.5% ammonium hydroxide in dichloromethane as the eluent. The fractions containing the pure *cis*-products were combined, concentrated under reduced pressure and dried on a lyophilizer to afford the cyclohexyl amine analogs of *cis*-1-

10 (4-aminocyclohexyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as white solids (see Table 1 for analytical details and isolated yields).

Table 1

Structure	Starting amine	Starting cyclohexanone scale (mmol)	<i>m/z</i> (MH ⁺)	HPLC RT (min)	Purity	% Isolated yield of <i>cis</i> -isomer
		5.08	429.0	5.63	95%	8
		7.62	417.0	5.96	100%	59
		7.62	373.0	5.32	100%	2

RP-HPLC analysis conditions: 5% to 85% acetonitrile/0.1M aqueous ammonium

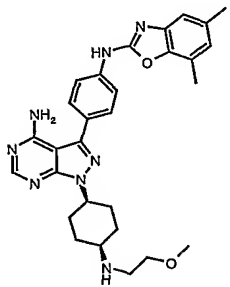
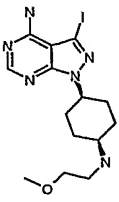
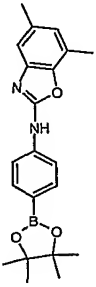
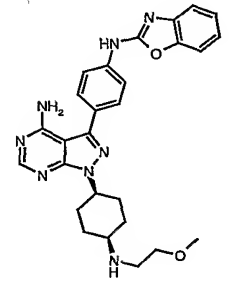
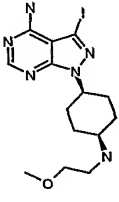
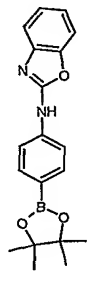
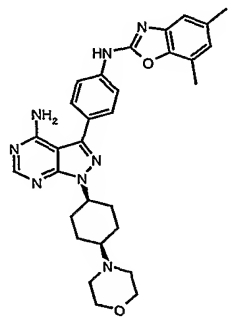
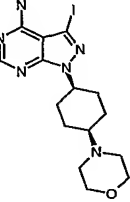
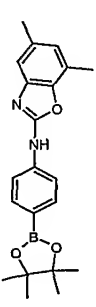
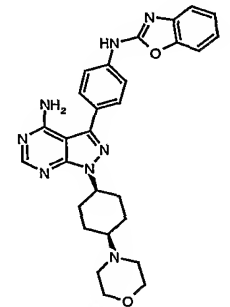
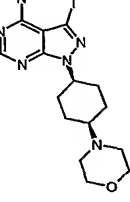
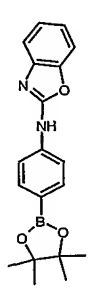
acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column.

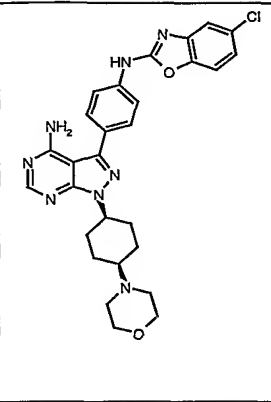
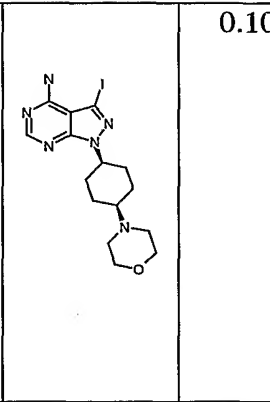
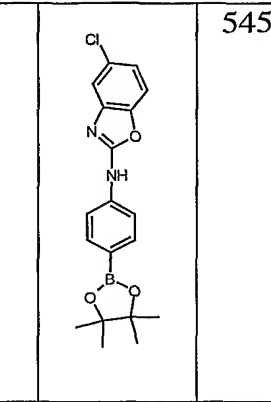
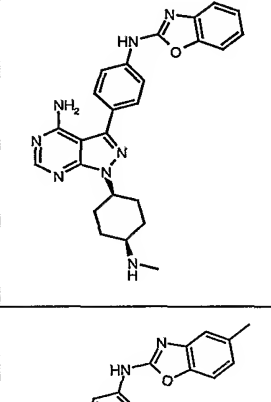
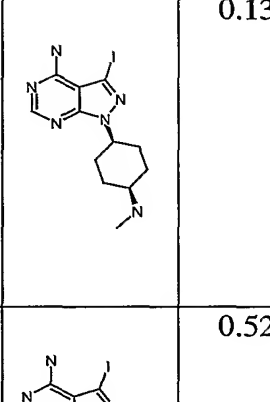
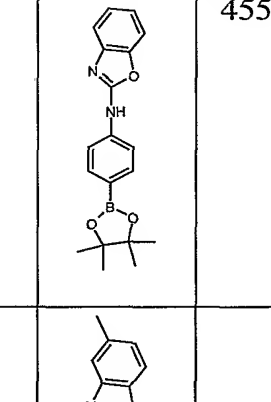
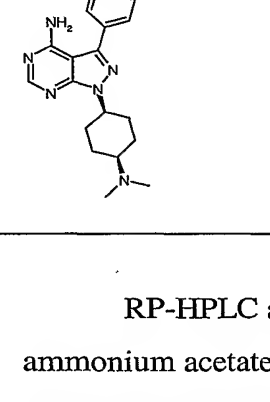
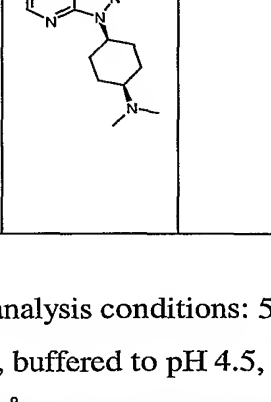
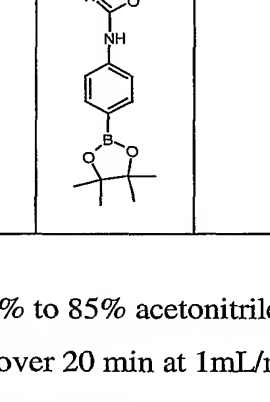
F. General synthesis of analogs of *cis-N2-4-[4-amino-1-(4-aminocyclohexyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-1,3-benzoxazol-2-amine*

The cyclohexylamine analog of *cis-1-(4-aminocyclohexyl)-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine* (0.10-0.52 mmol scale) was dissolved in ethylene glycol dimethylether (5-10 mL) and water (2.5-5 mL). The appropriate substituted or unsubstituted *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (1.25 equivalents), *tetrakis*(triphenylphosphine) palladium (0) (0.05 equivalents) and sodium carbonate (2.5 equivalents) were added and the reaction was heated at 80 °C for 20 hours. For the reactions which had not reached completion, additional boronate (1.25 equivalents) and palladium catalyst (0.05 equivalents) were added. In addition, DME/H₂O 2:1 (5 mL) was added to the reactions where precipitation had occurred and the reactions were re-subjected to heating at 80 °C for a further 22-40 hours. Silica gel (5-8 mL) was added to the reaction and the mixture was concentrated under reduced pressure. Purification via flash column chromatography over silica gel using a gradient of 2% to 50% methanol containing 0.5M ammonium hydroxide in dichloromethane yielded analogs of *cis-N2-4-[4-amino-1-(4-aminocyclohexyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl-1,3-benzoxazol-2-amine*. For products with unsatisfactory purity, the samples were further purified via RP-HPLC (Waters PrepLC 4000, flow rate: 10 mL/min, λ = 254 nm, gradient: 15% to 35% acetonitrile/0.1M aqueous ammonium acetate gradient over 40 minutes then 35% to 90% acetonitrile/0.1M aqueous ammonium acetate gradient over 150 minutes; Deltapak C18, 300Å, 15 μ m, 40 x 100 mm column). The fractions containing the desired products were combined and concentrated *in vacuo* then dried on a lyophilizer to afford the products as white or tan solids. (see Table 2 for analytical details and isolated yields).

Table 2

Ex.	Structure	Starting cyclohexyl amine	Starting boronate	<i>m/z</i> (MH ⁺)	HPLC RT (min)	Purity	% yield
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		structure	scale (mmol)					
614			0.24		527.3	11.66	100%	32
615			0.25		499.3	9.72	100%	79
616			0.33		539.3	11.50	100%	28
617			0.12		511.3	9.77	100%	60

618			0.10		545.2	11.36	97%	27
619			0.13		455.2	9.48	100%	61
620			0.52					

RP-HPLC analysis conditions: 5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μ m, 150 x 3.9 mm column.

- 5 Example 621: *cis*-N2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-(2-nitrophenyl)-1,3-thiazol-2-amine

The procedure described in the preparation of *cis*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine was employed with the exception that 2-bromo-2'-nitroacetophenone (0.126 g, 0.516 mmol) was used as the alkylating agent.

10 Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS

C18, 250 x 21 mm column, R_t 7.0-8.0 min) afforded *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-(2-nitrophenyl)-1,3-thiazol-2-amine as a yellow foam (0.088 g, 0.144 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 7.72 min; MS (MH)⁺ 611.

Example 622: *cis*-*N*2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzothiazol-2-amine

Pyridinium tribormide (0.894 g, 2.80 mmol) and 3,5-dimethylcyclohexanone (0.180 mL, 1.27 mmol) were suspended in dichloromethane (5 mL). The reaction mixture was stirred at ambient temperature for 24 h, then diluted with dichloromethane (60 mL). The organic layer was extracted sequentially with water (10 mL) and sodium bicarbonate (10 mL), dried (magnesium sulfate), filtered, and concentrated. Purification of the product by flash column chromatography (7.5% ethyl acetate/heptane) afforded 2,6-dibromo-3,5-dimethyl-1-cyclohexanone as a mixture of diastereomers (0.243 g, 0.855 mmol): TLC R_f (20% ethyl acetate/heptane): 0.35.

Alkylation of 2,6-dibromo-3,5-dimethyl-1-cyclohexanone (0.243 g, 0.855 mmol) was conducted using the alkylation procedure described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine, with the exception that the alkylation was conducted at 75 °C, to afford *N*-(4-bromophenyl)-*N*-(5,7-dimethyl-1,3-benzothiazol-2-yl)amine (0.251 g, 0.754 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 14.8 min.

N-(4-Bromophenyl)-*N*-(5,7-dimethyl-1,3-benzothiazol-2-yl)amine (0.251 g, 0.754 mmol) was converted to the title compound using the procedure described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous

ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.8-10.5 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzothiazol-2-amine as a white powder (0.081 g, 0.143 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 8.75 min; MS (MH)⁺ 568.

Examples 623: *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine

Cyclopentanone (200 μ L, 2.26 mmol) and pyridinium tribromide (0.723 g, 2.26 mmol) were suspended in dichloromethane (5 mL). The reaction mixture was stirred at ambient temperature overnight, then was diluted with ether/petroleum ether (1:1, 60 mL). The organic phase was extracted sequentially with water (10 mL) and aqueous sodium bicarbonate (10 mL), then was dried (magnesium sulfate), filtered, and concentrated. Purification of the product by flash column chromatography (25% ether/petroleum ether) afforded 2-bromocyclopentanone (0.220 g, 1.35 mmol) as a colorless oil; TLC (25% ether/petroleum ether) R_f : 0.35.

2-Bromocyclopentanone (0.220 g, 1.35 mmol) was converted to the title compound using the procedure described for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-(2-nitrophenyl)-1,3-thiazol-2-amine, except that the alkylation reaction was conducted at 60 °C. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 7.8-8.8 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine as a tan powder (0.009 g, 0.017 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 7.23 min; MS (MH)⁺ 530.

Example 624: *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-phenyl-1,3-thiazol-2-amine

The procedure for the preparation of *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine was used to convert butyrophenone (436 μ L, 3.00 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.9-11.1 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-phenyl-1,3-thiazol-2-amine as a white powder (0.022 g, 0.037 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 9.27 min; MS (MH)⁺ 594.

Example 625: *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine

The procedure described for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine was used to convert cyclohexanone (310 μ L, 3.00 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 6.8-8.6 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine as an orange powder (0.022 g, 0.040 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 7.62 min; MS (MH)⁺ 544.

Example 626: *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-isopropyl-4-phenyl-1,3-

thiazol-2-amine

The procedure described for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine was used to convert

- 5 isovalerophenone (0.484 g, 2.98 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 9.5-11.7 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-isopropyl-4-phenyl-1,3-thiazol-2-amine as a pink powder (0.060 g, 0.099 mmol);
- 10 RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 9.82 min; MS (MH)⁺ 608.

- 15 Example 627: *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-phenyl-5-propyl-1,3-thiazol-2-amine

- The procedure described for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine was used to convert valerophenone
- 20 (0.488 g, 3.01 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 9.6-11.8 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-phenyl-5-propyl-1,3-thiazol-2-amine as
- 25 a yellow powder (0.135 g, 0.222 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 10.08 min; MS (MH)⁺ 608.

- 30 Example 628: 3-[4-(1,3-Benzoxazol-2-ylmethyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
- 2-Aminophenol (0.257 g, 2.36 mmol) and 4-bromophenylacetic acid (0.500

g, 2.36 mmol) were heated neat in a sealed tube at 200 °C. After 4 h, the reaction mixture was cooled to ambient temperature and diluted with methanol/dichloromethane (5%, 60 mL). The organic phase was extracted with aqueous sodium carbonate (1 M, 10 mL), dried (magnesium sulfate), filtered, and concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate/heptane) afforded *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine as a brown solid (0.347 g, 1.20 mmol); (MH)⁺ 290.

N-(1,3-Benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine was converted to 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1,3-benzoxazole and then to the title compound using the procedure described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-chloro-1,3-benzothiazol-2-amine. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 5.6-7.3 min) afforded 3-[4-(1,3-benzoxazol-2-ylmethyl)phenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a white powder (0.102 g, 0.195 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 6.83 min; MS (MH)⁺ 523.

Example 629: *N*1-[2-(Dimethylamino)ethyl]-2-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}propanamide

The procedure described in the preparation of *N*1-[2-(dimethylamino)ethyl]-2-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanamide was employed, except that the Suzuki coupling procedure employed *N*-(1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 5.5-7.0 min) afforded *N*1-[2-(dimethylamino)ethyl]-2-{4-amino-3-[4-(1,3-benzoxazol-2-

ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}propanamide as an off-white solid (0.003 g, 0.006 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 6.70 min; MS (MH)⁺ 486.

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Example 630: *cis*-*N*2-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(4-methylphenyl)-1,3-thiazol-2-amine

p-Tolylboronic acid (0.150 g, 1.10 mmol), tetrakis(triphenylphosphine)pal-
ladium(0) (0.064 g, 0.055 mmol), and cesium carbonate (1.80 g, 5.52 mmol) were
suspended in toluene (25 mL). The reaction mixture was purged under a vigorous
flow of nitrogen for 15 minutes. Butyryl chloride (0.344 mL, 3.31 mmol) was
added, and the reaction mixture was heated at 100 °C under an atmosphere of
nitrogen for 24 h. The reaction mixture was cooled to ambient temperature and
diluted with ether (100 mL). The organic layer was extracted sequentially with
water (10 mL), aqueous sodium bicarbonate (10 mL), and aqueous sodium chloride
(10 mL). The organic layer was dried (magnesium sulfate), filtered, and
concentrated. Purification of the residue by flash column chromatography (7.5 %
ether/petroleum ether) afforded 1-(4-methylphenyl)-1-butanone as a colorless oil
(0.134 g, 0.827 mmol): ¹H NMR (CDCl₃, 400 MHz) δ 7.86 (d, 2H), 7.25 (d, 2H),
2.92 (t, 2H), 2.41 (s, 3H), 1.76 (sx, 2H), 1.00 (t, 3H).

1-(4-Methylphenyl)-1-butanone (0.134 g, 0.827 mmol) was converted to the
title compound using the procedure described in the preparation of *cis*-*N*2-(4-{4-
amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-
yl}phenyl)-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]thiazol-2-amine. Purification of the
product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium
acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm
column, R_t 10.0-12.0 min) afforded *cis*-*N*2-(4-{4-amino-1-[4-(4-
methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-
(4-methylphenyl)-1,3-thiazol-2-amine as an off-white solid (0.036 g, 0.059 mmol);
RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10
min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 10.13

min; MS (MH)⁺ 608.

Example 631: *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(2-methylphenyl)-1,3-thiazol-2-amine

The procedure described for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(4-methylphenyl)-1,3-thiazol-2-amine was used to convert *o*-tolylboronic acid (0.200 g, 1.47 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 9.8-11.7 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(2-methylphenyl)-1,3-thiazol-2-amine as an off-white solid (0.075 g, 0.123 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 9.83 min; MS (MH)⁺ 608.

Example 632: *cis-N2*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(3-methylphenyl)-1,3-thiazol-2-amine

The procedure described for *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(4-methylphenyl)-1,3-thiazol-2-amine was used to convert *m*-tolylboronic acid (0.175 g, 1.29 mmol) to the title compound. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 10.0-12.0 min) afforded *cis-N2*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-4-(3-methylphenyl)-1,3-thiazol-2-amine as an off-white solid (0.051 g, 0.084 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 10.13 min; MS (MH)⁺ 608.

Example 633: *Cis-N2*-{4-(4-amino-1-(4-(4-methylpiperazino)cyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1*H*-2-indolecarboxamide bismaleate

A mixture of *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.50 g, 1.15 mmol) in dichloromethane (4 mL) and pyridine (4 mL) was cooled to 0°C then treated with 1*H*-2-indolecarbonyl chloride (0.27 g, 1.49 mmol) in dichloromethane (4 mL). The mixture was allowed to warm to ambient temperature and stirred for one hour. The solvents were evaporated under reduced pressure then the residue was partitioned between dichloromethane (50 mL) and 1 N aqueous sodium hydroxide. The layers were separated then the organic solution was dried over magnesium sulfate, filtered and the filtrate concentrated under reduced pressure to yield a residue which was purified by flash chromatography on silica using dichloromethane-methanol (7:3) as mobile phase. The solid (0.53 g) was dissolved in ethyl acetate (60 mL) and ethanol (35 mL) by warming to 60°C. Maleic acid (0.32 g, 2.75 mmol) in ethyl acetate (5 mL) was added then the mixture was cooled to 0°C. The solid which formed was collected by filtration to give (0.70 g, 0.86 mmol) *Cis-N2*-{4-(4-amino-1-(4-(4-methylpiperazino)cyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1*H*-2-indolecarboxamide bismaleate: ¹H NMR (DMSO-*d*₆, 400MHz) δ 11.82 (s, 1H), 9.46 (s, 1H), 8.26(s, 1H), 8.10 (d, 1H), 7.68 (d, 1H), 7.48 (d, 1H), 7.40 (s, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 7.24 (t, 1H), 7.09 (t, 1H), 6.14 (s, 4H), 4.88 (m, 1H), 3.97 (s, 3H), 2.3-3.3 (m, 14H), 2.09 (m, 2H), 1.7-1.8 (m, 4H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) *t*_r 15.22 min; MS:MH⁺ 580.3.

Example 634: *Cis-N2*-{4-(4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide bismaleate

The title compound was prepared from *cis*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and 1-methyl-1*H*-2-indolecarbonyl chloride in a similar manner as described for the

- preparation of *Cis-N2*-{4-(4-amino-1-(4-(4-methylpiperazino)cyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl}-1*H*-2-indolecarboxamide bismaleate: ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.47 (s, 1H), 8.26(s, 1H), 8.09 (d, 1H), 7.71 (d, 1H), 7.59 (d, 1H), 7.17-7.36 (m, 4H), 7.16 (t, 1H), 6.16 (s, 4H), 4.88 (m, 1H), 3.96 (s, 3H), 2.3-3.3 (m, 14H), 2.09 (m, 2H), 1.7-1.8 (m, 4H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μ m, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) *t*_r 15.98 min; MS:MH⁺ 594.3.
- 10 Example 635: *N1*-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide acetate
- A. 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline
- A mixture of *tert*-butyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (45.0 g, .129 mol) was dissolved in
- 15 dichloromethane (270 mL) then the solution was cooled to 5°C in an ice bath. A mixture of 20% trifluoroacetic acid in dichloromethane was added dropwise over the course of one hour while maintaining the temperature of the mixture at <5°C. The reaction mixture was warmed to ambient temperature and stirred for 2 hours. The solvents were removed under reduced pressure then the resulting oil was dissolved
- 20 in dichloromethane (250 mL) and cautiously extracted with 2.5 N aqueous sodium hydroxide (300 mL) then brine (100 mL). The organic solution was dried over magnesium sulfate, filtered and the filtrate concentrated under reduced pressure to give 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (21.7 g, 67.5%) as a light brown solid bismaleate: ¹H NMR (DMSO-*d*₆, 400MHz) δ 7.06 (d, 1H), 6.98 (s, 1H), 8.09 (d, 1H), 6.59 (d, 1H), 5.13 (bs, 2H), 3.76 (s, 3H), 1.26 (s, 12H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μ m, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) *t*_r 10.85 min.
- 30 B. *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate
- A mixture of *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-